21 July 2022
EMA/686052/2022
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Ultomiris

International non-proprietary name: ravulizumab

Procedure No. EMEA/H/C/004954/II/0026

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| Abbreviation or Term | Definition |
|---|---|
| AChR | acetylcholine receptor |
| ADA | antidrug antibody |
| ADL | activities of daily life |
| aHUS | atypical hemolytic uremic syndrome |
| ARDS | acute respiratory distress syndrome |
| C5 | complement component 5 |
| CI | confidence interval |
| COVID-19 | coronavirus disease 2019 |
| CSF | cerebrospinal fluid |
| EMA | European Medicines Agency |
| FDA | (the US) Food and Drug Administration |
| gMG | generalized myasthenia gravis |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IST | immunosuppressant therapy |
| IV | intravenous(ly) |
| IVIg | intravenous immunoglobulin |
| LS | least squares |
| mAb | monoclonal antibody |
| MAC | membrane attack complex |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MG-ADL | Myasthenia Gravis Activities of Daily Living |
| MGFA | Myasthenia Gravis Foundation of America |
| MGFA-PIS | Myasthenia Gravis Foundation of America Post-Intervention Status |
| MG-QoL15r | Revised Myasthenia Gravis Quality of Life 15-item scale |
| MMRM | mixed-effects model for repeated measures |
| MMS | Minimal manifestation status |
| MuSK | muscle-specific kinase |
| Neuro-QoL | Neurological Quality of Life |
| NMJ | neuromuscular junction |
| NMOSD | Neuromyelitis Optica Spectrum Disorder |
| PD | pharmacodynamic(s) |
| PE | plasma exchange |
| PK | pharmacokinetic(s) |
| PMDA | Pharmaceuticals and Devices Agency (Japan) |
| PNH | paroxysmal nocturnal hemoglobinuria |
| PP | plasmapheresis |
| PY | patient years |
| q2w | every 2 weeks |
| q8w | every 8 weeks |
| QMG | Quantitative Myasthenia Gravis score for disease severity |
| REMS | Risk Evaluation and Mitigation Strategy |
| SAE | serious adverse event |
| SD | standard deviation |
| SMQ [N]/narrow SMQ | standardised MedDRA query (narrow) |
| SOC | System Organ Class |
| TEAE | treatment-emergent adverse event |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Alexion Europe SAS submitted to the European Medicines Agency on 19 November 2021 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include treatment of adult patients with generalized myasthenia gravis (gMG). As a consequence, Sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 and 6.6 of the SmPC and corresponding sections in the Package Leaflet are updated accordingly. The RMP has been updated to version 4.0 to align with the indication extension. Lastly, the minor editorial corrections are made throughout the SmPc and package leaflet. The Applicant also requested 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision P/0230/2021 on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for ravulizumab (Ultomiris), (EMEA-001943-PIP03-20).

The waiver applies to:

- the paediatric population from birth to less than 6 years of age;
- concentrate for solution for infusion, intravenous use;
- on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset(s).

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

## Derogation(s) of market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application submitted a claim addressing the following derogation laid down in Article 8.3 of the same Regulation; the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the MAH.

### *MAH request for additional market protection*

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

### *Scientific advice*

The MAH did not seek Scientific Advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: N/A

| Timetable | Actual dates |
|---|---|
| Submission date | 19 November 2021 |
| Start of procedure: | 25 December 2021 |
| CHMP Rapporteur Assessment Report | 1 March 2022 |
| PRAC Rapporteur Assessment Report | 25 February 2022 |
| PRAC members comments | 2 March 2022 |
| CHMP Co-Rapporteur Critique | 10 March 2022 |
| PRAC Outcome | 10 March 2022 |
| CHMP members comments | 14 March 2022 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 17 March 2022 |
| Request for supplementary information (RSI) | 24 March 2022 |
| CHMP Rapporteur Assessment Report | 31 May 2022 |
| PRAC Outcome | 10 June 2022 |
| CHMP members comments | 13 June 2022 |
| Updated CHMP Rapporteur Assessment Report | 17 June 2022 |
| Request for supplementary information (RSI) | 23 June 2022 |
| CHMP Rapporteur Assessment Report | 6 July 2022 |
| CHMP members comments | 14 July 2022 |
| Updated CHMP Rapporteur Assessment Report | 15 July 2022 |
| Opinion | 21 July 2022 |
| The CHMP adopted a report on similarity of Ultomiris with Soliris (Eculizumab) and Vyvgart (efgartigimod alfa) on | 21 July 2022 |
| The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Ultomiris in comparison with existing therapies on | 21 July 2022 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

### *Disease or condition*

The initially claimed therapeutic indication was:

*"The treatment of adult patients with anti-acetylcholine receptor (AChR) antibody-positive generalized myasthenia gravis (gMG) with remaining symptomatology despite at least one immunomodulatory therapy (see section 5.1).*

Myasthenia gravis (gMG) is a rare, chronic, neuromuscular autoimmune disease mediated by pathogenic immunoglobulin G (IgG) autoantibodies, binding to acetylcholine receptors or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction (NMJ), which causes debilitating and potentially life-threatening muscle weakness.

### *Epidemiology*

In about two-thirds of patients, the first symptom is weakness of extrinsic ocular muscles. In 1 of 10 MG patients, symptoms remain limited to extrinsic ocular muscles (ocular myasthenia gravis). However, in more than 80% of patients, the symptoms progress within 2 years to affect other bulbar muscles as well as limb muscles (generalised MG). The generalized muscle weakness leads to difficulties in mobility, speech, swallowing, and vision, as well as impaired respiratory function and extreme fatigue. Up to 20% of patients experience potentially life-threatening myasthenic crisis, with respiratory failure requiring mechanical ventilation.

The disease presents with two peaks of incidence, below or above the age of 50, termed early-onset MG and late-onset MG, respectively. The prevalence of MG in the European Union is estimated at 3.7 in 10,000, equivalent to a total of around 191,000 people[1] .

### *Aetiology and pathogenesis*

MG is caused by pathogenic autoantibodies that interfere with synaptic transmission at the neuromuscular junction and impair or prevent muscle contraction[2,3,4]. In approximately 85% of cases, circulating antibodies target the acetylcholine receptor (AChR) itself. In the remaining 15%, approximately half have antibodies against muscle-specific tyrosine kinase (MuSK), while the other half

[1] EMA 2017 Recommendation for maintenance of orphan designation at the time of addition of a new indication to the marketing authorization Soliris (eculizumab) for the treatment of myasthenia gravis. https://www.ema.europa.eu/documents/orphan-review/recommendation-maintenance-orphandesignation-time-addition-new-indication-marketing-authorisation_en.pdf
[2] Gilhus, N. E., & Verschuuren, J. J. (2015). Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurology, 14(10), 1023-1036.
[3] Gilhus, N. E. (2016a). Myasthenia Gravis. New England Journal of Medicine, 375(26), 2570-2581.
[4] Gilhus, N. E., Skeie, G. O., Romi, F., Lazaridis, K., Zisimopoulou, P., & Tzartos, S. (2016b). Myasthenia gravis - autoantibody characteristics and their implications for therapy. Nature Reviews: Neurology, 12(5), 259-268.

may be positive for autoantibodies against lipoprotein-related protein receptor 4 (LRP4) or other antigens associated with the neuromuscular junction[5,6].

The pathogenic actions of IgG autoantibodies include functional blockade of AChR, accelerated internalization and degradation of AChR, and activation of the complement system. These pathogenic actions result in reduced density of functional AChR and simplification of the NMJ, leading to failure of neuromuscular transmission. Anti-AChR autoantibodies are of the IgG1 and IgG3 subtypes. Anti-MuSK autoantibodies are IgG4 subtype and do not activate the complement pathway[7].

## *Clinical presentation, diagnosis and stage/prognosis*

MG is an autoimmune disease characterized by muscle weakness that fluctuates, worsening with exertion, and improving with rest. In most cases, initial symptoms are ocular and include ptosis and diplopia, but within 2 to 3 years of onset, the disease usually worsens, and other muscles become affected; this is referred to as generalized MG (gMG)[8]. Additional symptoms typically include difficulty chewing, dysphagia, dysarthria, hypophonia, dyspnea, difficulty holding the head upright, and fatigue, marked reductions in the ability to perform activities of daily living (ADLs), extreme fatigue, and episodes of pulmonary failure requiring mechanical ventilation[9] [10].

Hospitalizations for gMG exacerbations are common, with the need for respiratory support, including mechanical ventilation secondary to respiratory failure (eg, myasthenic crisis) with no substantial improvement in mortality or length of hospitalization over time.

The Myasthenia Gravis Foundation of America (MGFA) Clinical Classification categorizes patients according to clinical evaluation, which in increasing severity can be: ocular MG; mild, moderate, severe generalized symptoms of MG; MG that requires intubation[11].

The diagnosis of myasthenia gravis is confirmed by the combination of relevant symptoms and signs, a positive test for specific autoantibodies and a positive neurophysiological examination, including repetitive nerve stimulation or single-fiber electromyography, and symptomatic improvement following treatment with acetylcholinesterase (AChE) inhibitors.

## *Management*

Current treatment options include acetylcholinesterase inhibitors and long-term immune therapies with immunosuppressive agents such as corticosteroids, azathioprine, cyclosporine, and mycophenolate, but tacrolimus, methotrexate, and cyclophosphamide are also used. Thymectomy is also a treatment option. Monoclonal antibodies such as rituximab are used. Eculizumab, an anti-C5 treatment, was approved in the EU for the treatment of patients with refractory gMG and who are AChR-Ab seropositive. Plasmapheresis/plasma exchange (PLEX) and intravenous immunoglobulins (IVIg) are mostly used as rescue therapies in situations of clinical deterioration[12].

[5] Meriggioli, M. N., & Sanders, D. B. (2012). Expert Review of Clinical Immunology, 8(5), 427-438.
[6] Zhang, B. et al. (2012). Archives of Neurology, 69(4), 445-451.
[7] Howard JF et al. Lancet Neurol 2017;16:976-86.
[8] Trouth AJ, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Autoimmune Dis. 2012; 2012: 874680.
[9] Juel C et al. Orphanet J Rare Dis. 2007
[10] Meriggoli MN and Sanders DB. Lancet Neurol. 2009 May; 8(5): 475–490.
[11] Jaretzki A et al. Neurology 2000;55:16-23.
[12] Mantegazza R et al. Immunotargets Ther. 2020; 9: 317–331.

At the time of this application, with the exception of AChE inhibitors, corticosteroids, the complement inhibitor eculizumab (Soliris), and azathioprine (Jayempi), which have received regulatory approval for the treatment of gMG, all other existing therapies are used off-label.

Patients with AChR-Ab seronegative gMG have greater limitations on treatment options, as AChE inhibitors are known to have reduced efficacy in this population and eculizumab is approved only for AChR-Ab seropositive patients and is limited to treatment of refractory MG.

### 2.1.2. About the product

Ravulizumab (Ultomiris, ALXN1210) is a humanized monoclonal antibody (mAb) that binds to complement component 5 (C5) and blocks its activation by complement pathway convertases.

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA43

Currently, Ultomiris is approved for Paroxysmal Nocturnal Hemoglobinuria (PNH) and atypical Haemolytic Uremic Syndrome (aHUS):

*Ultomiris is indicated in the treatment of adult and paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH)*

- *in patients with haemolysis with clinical symptom(s) indicative of high disease activity.*
- *in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months (see section 5.1).*

*Ultomiris is indicated in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab (see section 5.1).*

Ravulizumab, derived through targeted engineering from eculizumab (h5G1.1-mAb; Soliris), is a terminal complement inhibitor that specifically binds to C5 with high affinity, inhibiting the enzymatic cleavage of C5 into C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]). By binding specifically to C5, ravulizumab antagonizes terminal complement-mediated inflammation, cell activation, and cell lysis. This mechanism of action provides a therapeutic rationale for the use of ravulizumab in diseases in which activation of terminal complement plays an etiologic role.

### 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Not applicable.

### 2.1.4. General comments on compliance with GCP

The clinical trial was performed in accordance with GCP as claimed by the MA.

## *2.2. Non-clinical aspects*

No additional nonclinical data with ravulizumab have been generated for this application.

Direct testing of ravulizumab in non-clinical models of Myasthenia Gravis (MG) is precluded by ravulizumab being a highly specific monoclonal antibody that binds only to human C5.

A summary of results from relevant published studies has been submitted.

In MG, complement activation initiates an inflammatory cascade that induces blockade of neuromuscular transmission and resulting in skeletal muscle weakness[13]. Published nonclinical experiments of MG have demonstrated that uncontrolled complement activation leads to membrane attack complex (MAC) deposition at the neuromuscular junction (NMJ) and impairment of the neuromuscular transmission in anti-AChR antibody-positive MG[14 15 16 17]. The pro-inflammatory properties of the activated terminal complement components, C5a and C5b 9, have been implicated in a wide range of inflammatory disease states[18]. Data presented supports terminal C5 inhibition with anti-C5 mAb, such as ravulizumab, as a viable therapeutic approach for patients with MG.

## 2.2.1. Ecotoxicity/environmental risk assessment

According to the CHMP guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted of environmental risk assessment because, due to their nature they are unlikely to result in significant risk to the environment. Due to the fact that ravulizumab is a monoclonal antibody and thus a protein, no Environmental Risk Assessment is provided for this application which was considered acceptable by CHMP.

## 2.2.2. Discussion on non-clinical aspects

No additional nonclinical data with ravulizumab have been generated for this application since the dose and administration route proposed for this new indication of gMG is the same that was previously approved for atypical haemolytic uremic syndrome (aHUS) and paroxysmal nocturnal haemoglobinuria (PNH) indications. This was considered acceptable by CHMP.

## 2.2.3. Conclusion on the non-clinical aspects

A full nonclinical package was provided as part of the initial marketing authorisation application (MAA) for Ultomiris in 2018. With the exception of the published studies discussed above, no additional nonclinical data have been generated. This is considered acceptable by CHMP.

Considering the above data, ravulizumab is not expected to pose a risk to the environment.

The non-clinical data available supports the use of Ultomiris in the approved indication.

[13] Jacob S. Myasthenia Gravis – A Review of Current Therapeutic Options. European neurological review. DOI:10.17925/ENR.2018.13.2.86.
[14] Engel AG, Lambert EH, Howard FM. Immune complexes (IgG and C3) at the motor end-plate in myasthenia gravis: ultrastructural and light microscopic localization and electrophysiologic correlations. Mayo Clinic Proceedings. 1977 May;52(5):267-280. PMID: 870771
[15] Sahashi K, Engel AG, Lambert EH, Howard FM Jr. Ultrastructural localization of the terminal and lytic ninth complement component (C9) at the motor end-plate in myasthenia gravis. J Neuropathol Exp Neurol. 1980 Mar;39(2):160-72. doi: 10.1097/00005072-198003000-00005. PMID: 7373347.
[16] Nakano S, Engel AG. Myasthenia gravis: quantitative immunocytochemical analysis of inflammatory cells and detection of complement membrane attack complex at the end-plate in 30 patients. Neurology. 1993 Jun;43(6):1167-72. doi: 10.1212/wnl.43.6.1167. PMID: 8170563.
[17] Tüzün E, Scott BG, Goluszko E, Higgs S, Christadoss P. Genetic evidence for involvement of classical complement pathway in induction of experimental autoimmune myasthenia gravis. J Immunol. 2003 Oct 1;171(7):3847-54. doi: 10.4049/jimmunol.171.7.3847. PMID: 14500686.
[18] Matis, L., Rollins, S. Complement-specific antibodies: Designing novel anti-inflammatories. *Nat Med* **1,** 839–842 (1995). https://doi.org/10.1038/nm0895-839

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

**Table 1 – Tabular overview of clinical studies**

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s)<br><br>Dosage Regimen<br><br>Route of Administration | Number of Subjects<br><br>(Planned/ Treated) | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status<br><br>Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy and Safety | ALXN1210-MG-306 | M5.3.5.1 | To assess the efficacy, safety, immunogenicity, PK, PD, safety, and efficacy in adult patients with gMG | Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study with an ongoing Open-Label Extension Period of up to 2 years in adult patients with gMG who were naïve to complement inhibitor treatment | **Primary Evaluation Period (Day 1):**<br>Ravulizumab IV weight-based loading[a] dose on Day 1 and weight-based maintenance[b] dose starting on Day 15 and q8w thereafter<br><br>Placebo<br>Matched dosing to ravulizumab IV<br><br>Blinded loading dose (900 mg) for all patients at Week 26<br><br>**Extension Period (Week 28):**<br>Ravulizumab IV weight-based maintenance dose[b] q8w | 160/175<br><br>Ravulizumab 80/86<br><br>Placebo 80/89 | Adult patients with gMG | 26-week Randomized-Controlled Period followed by Open-Label Extension Period of up to 2 years | Ongoing Open-Label Extension Period (Randomized-Controlled Period Completed)<br><br>Primary Analysis CSR |

[a] Ravulizumab loading dose: 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg.
[b] Ravulizumab maintenance dose: 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg.
Abbreviations: CSR = clinical study report; gMG = generalized myasthenia gravis; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; q8w = once every 8 weeks

### 2.3.2. Pharmacokinetics

Data from a Phase 3 study of patients with gMG (Study ALXN1210-MG-306) are incorporated in the current clinical pharmacology analyses. Only data collected during the Randomized-Controlled Period are included. Durations of PK, PD, and immunogenicity data coverage and data cut-off dates for Study ALXN1210-MG-306 are summarized in Table 2.

**Table 2 - Summary of PK, PD, and Immunogenicity Data for the Ravulizumab gMG Development Program**

| Study Identifier: (Population Studied) | Study Description | Number of Patients | Duration of PK, PD, and ADA Data Coverage | PK, PD, and Immunogenicity Data Cutoff Date for Pooled Analysis |
|---|---|---|---|---|
| ALXN1210-MG-306 (Adult complement inhibitor treatment-naïve patients with gMG) | Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the efficacy, PK, PD, immunogenicity, and safety of ravulizumab IV | 175[a] | RCP: Up to Day 183 | All PK, PD, and immunogenicity data through the RCP included for the PK Analysis Set, Full Analysis Set, and Safety Set, respectively; data cutoff: 11 May 2021 |

[a] The same number of patients were included in the PK Analysis Set, the Full Analysis Set, and the Safety Set.
Abbreviations: ADA = antidrug antibody; gMG = generalized myasthenia gravis; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; RCP = Randomized-Controlled Period

Table 3 summarizes the dosing and sampling schedules for Study ALXN1210-MG-306.

**Table 3 - Dosing and Sampling Schedules for the Randomized-Controlled Period (Study ALXN1210-MG-306)**

| Parameter | Dosing and Sampling Schedules |
|---|---|
| Dosing regimen | Ravulizumab IV 10 mg/mL body weight-based dosing:<br>Patients weighing ≥ 40 to < 60 kg: loading dose 2400 mg on Day 1, maintenance dose 3000 mg on Days 15, 71, and 127<br>Patients weighing ≥ 60 to < 100 kg: loading dose 2700 mg on Day 1, maintenance dose 3300 mg on Days 15, 71, and 127<br>Patients weighing ≥ 100 kg: loading dose 3000 mg on Day 1, maintenance dose 3600 mg on Days 15, 71, and 127<br>Patients in the placebo group received equivalent dosing with placebo. |
| PK and PD (serum free C5) | Within 30 minutes before start of infusion (predose) on Days 1, 15, 71, 127, and 183; and within 30 minutes after completion of infusion (post dose) on Days 1, 15, 71, and 127.<br>In the event of clinical deterioration, blood samples were to be obtained for PK and PD. |
| Immunogenicity (ADA) | Within 30 minutes before start of infusion (predose) on Days 1, 15, 71, 127, and 183.<br>In the event of clinical deterioration, blood samples were to be obtained for ADAs. |

Note: Day 1 refers to start of dosing.
Abbreviations: ADA = antidrug antibody; C5 = complement component 5; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics

## *Absorption*

Ravulizumab is intended to be administered intravenously which results in 100% bioavailability. The $t_{max}$ is expected at the end of infusion or soon after end of infusion. Over the studied dose and regimen range, ravulizumab exhibited dose proportional and time linear PK.

## *Distribution*

The mean (SD) Vss in adult patients with gMG is 5.74 (1.16) L.

## *Elimination*

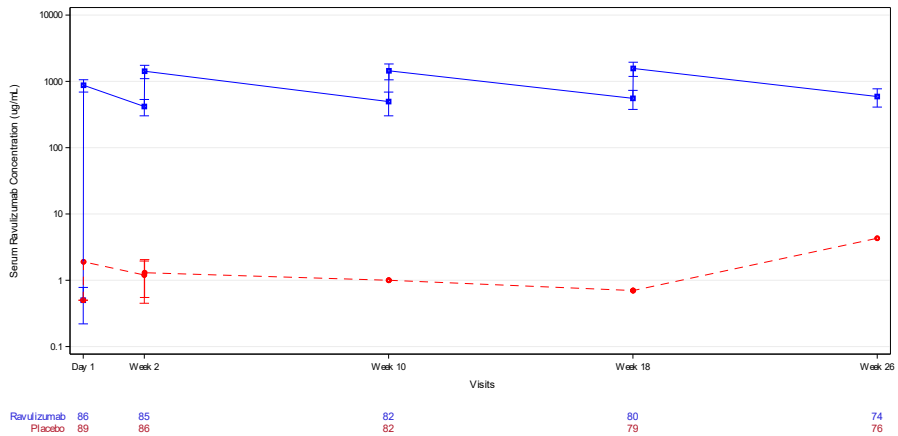
As an IgG monoclonal antibody, ravulizumab is expected to be metabolized in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and is subject to similar elimination. Ravulizumab contains only natural occurring amino acids and has no known active metabolites. The mean (SD) $t_{½}$ and CL of ravulizumab in adult patients with gMG is 56.6 (8.36) days and 0.00313 (0.000996) L/h, respectively.

## *Pharmacokinetics in the target population*

Exploratory PK data

The mean (SD) ravulizumab serum concentration versus time profile (semi-log scale) is presented in Figure 1.

**Figure 1 - Mean (SD) Ravulizumab Serum Concentration, Semi-Log Scale (Study ALXN1210-MG-306 PK Analysis Set)**




Note: For ravulizumab concentrations that were BLQ of < 1.00 or < 4.00 µg/mL (depending on degree of sample dilution), LLOQ/2 = 0.50 or 2.00 µg/mL were utilized, respectively.
Abbreviations: BLQ = below the limit of quantitation; LLOQ = lower limit of quantitation; PK = pharmacokinetic; SD = standard deviation

Pharmacokinetic parameters for ravulizumab during the Randomized-Controlled Period are summarized by dosing interval in Table 4 and Table 5 for the loading and last maintenance doses, respectively.

**Table 4: Ravulizumab PK Parameters Following the First (Loading) Dose (Study ALXN1210-MG-306 PK Analysis Set)**

| Parameter | Statistics | All Patients | ≥ 40 to < 60 kg | ≥ 60 to < 100 kg | ≥ 100 kg |
|---|---|---|---|---|---|
| $C_{max}$ (µg/mL) | n | 86 | 7 | 47 | 32 |
| | Mean (SD) | 874.1 (184.24) | 1054.3 (163.57) | 912.1 (170.39) | 778.8 (160.96) |
| | CV% | 21.1 | 15.5 | 18.7 | 20.7 |
| | Median (min, max) | 836.0 (399, 1420) | 1060.0 (778, 1310) | 868.0 (692, 1420) | 779.5 (399, 1350) |
| | n | 85 | 7 | 46 | 32 |

**Table 4: Ravulizumab PK Parameters Following the First (Loading) Dose (Study ALXN1210-MG-306 PK Analysis Set)**

| Parameter | Statistics | All Patients | ≥ 40 to < 60 kg | ≥ 60 to < 100 kg | ≥ 100 kg |
|---|---|---|---|---|---|
| $C_{trough}$ (µg/mL) | Mean (SD) | 417.8 (115.51) | 555.7 (116.45) | 438.5 (118.11) | 357.8 (68.12) |
| | CV% | 27.6 | 21.0 | 26.9 | 19.0 |
| | Median (min, max) | 397.0 (234, 1000) | 520.0 (451, 751) | 422.0 (305, 1000) | 339.0 (234, 570) |

Abbreviations: Cmax = maximum observed serum concentration; Ctrough = concentration at the end of the dosage interval; CV = coefficient of variation; max = maximum; min = minimum; PK = pharmacokinetics; SD = standard deviation

**Table 5: Ravulizumab PK Parameters Following the Final Maintenance Dose (Study ALXN1210-MG-306 PK Analysis Set)**

| Parameter | Statistics | All Patients | ≥ 40 to < 60 kg | ≥ 60 to < 100 kg | ≥ 100 kg |
|---|---|---|---|---|---|
| $C_{max}$ (µg/mL) | n | 76 | 4 | 43 | 29 |
| | Mean (SD) | 1548.3 (359.43) | 2015.0 (345.40) | 1645.3 (337.63) | 1340.1 (267.95) |
| | CV% | 23.2 | 17.1 | 20.5 | 20.0 |
| | Median (min, max) | 1500.0 (810, 2510) | 1900.0 (1750, 2510) | 1660.0 (1060, 2410) | 1340.0 (810, 1990) |
| $C_{trough}$ (µg/mL) | n | 70 | 4 | 39 | 27 |
| | Mean (SD) | 586.6 (173.91) | 887.3 (82.72) | 635.7 (157.28) | 471.3 (109.47) |
| | CV% | 29.6 | 9.3 | 24.7 | 23.2 |
| | Median (min, max) | 570.0 (211, 1030) | 866.5 (817, 999) | 649.0 (241, 1030) | 456.0 (211, 635) |

Note: Data were excluded for patients after they received a supplemental dose following PE, PP, or IVIg.
Abbreviations: Cmax = maximum observed serum concentration; Ctrough = concentration at the end of the dosage interval; CV = coefficient of variation; IVIg = intravenous immunoglobulin; max = maximum; min = minimum; PE = plasma exchange; PK = pharmacokinetics; PP = plasmapheresis; SD = standard deviation

Population PK model

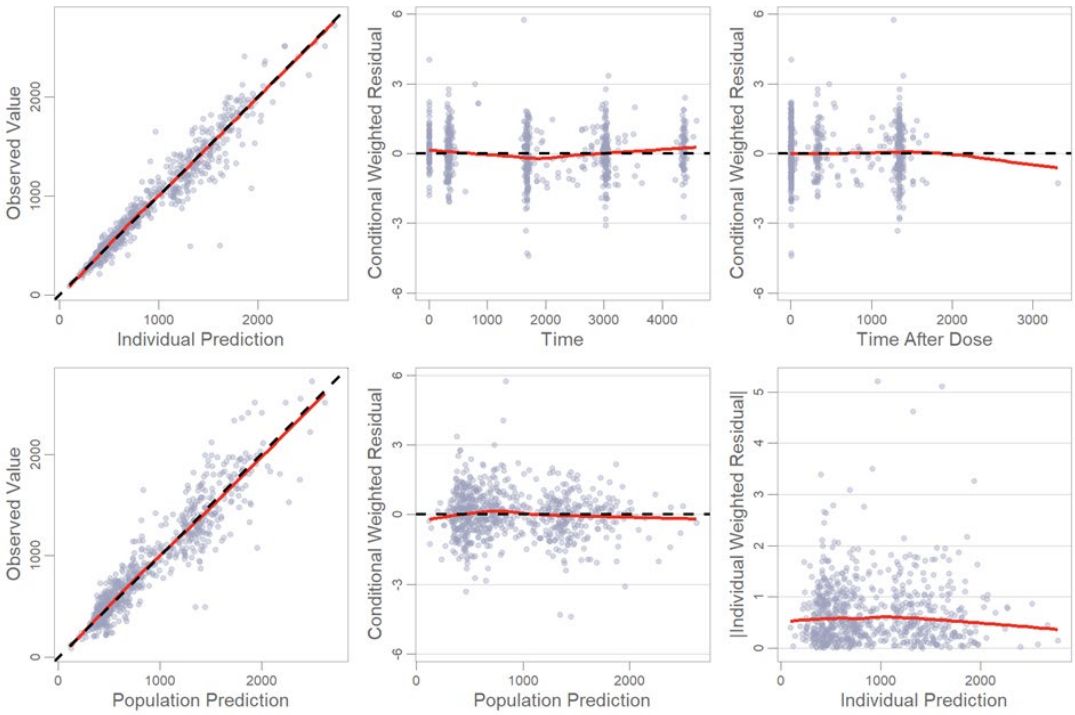
A Pop-PK analysis was previously performed to assess concentration-time profiles of ravulizumab following IV administration in healthy subjects and patients with PNH. A 2-compartment model with linear clearance adequately characterized the concentration-time profiles of ravulizumab. The Pop-PK analysis included 38 (12.7%) healthy subjects and 261 (87.3%) patients with PNH. The Pop-PK model in patients with PNH included the effect of body weight on all clearance and volume parameters (CL, Q, Vc, and Vp). In addition, the Pop-PK model included the effect of BMI on volume of distribution parameters (Vc and Vp). Finally, the PNH model included the effect of hemoglobin on central parameters (CL and Vc).

Rescue therapy (e.g, high-dose corticosteroid, PE/PP, or IVIg) was allowed if a patient experienced clinical deterioration as defined in the protocol for Study ALXN1210-MG-306. PE/PP interventions are expected to result in the bulk removal and replacement of plasma, thereby removing pathologic substances such as pathologic antibodies, immune complexes, and cytokines, as well as ravulizumab. Also, IVIg treatment is expected to competitively bind the endosomal neonatal Fc receptor recycling mechanism of monoclonal antibodies and, thus, inhibit neonatal recycling of ravulizumab, resulting in reduced serum ravulizumab concentration[19]. Thus, supplemental dosing of study drug was implemented in Study ALXN1210-gMG-306 if PE/PP or IVIg rescue therapy was administered. As a result, the Pop-PK

[19] Fitzpatrick AM, Mann CA, Barry S, Brennan K, Overell JR, Willison HJ. An open label clinical trial of complement inhibition in multifocal motor neuropathy. J Peripher Nerv Syst 2011; 16(2): 84-91

base model was developed to account for additional pathways of elimination of ravulizumab as a potential effect of PE/PP or IVIg and supplemental doses administered secondary to these interventions.

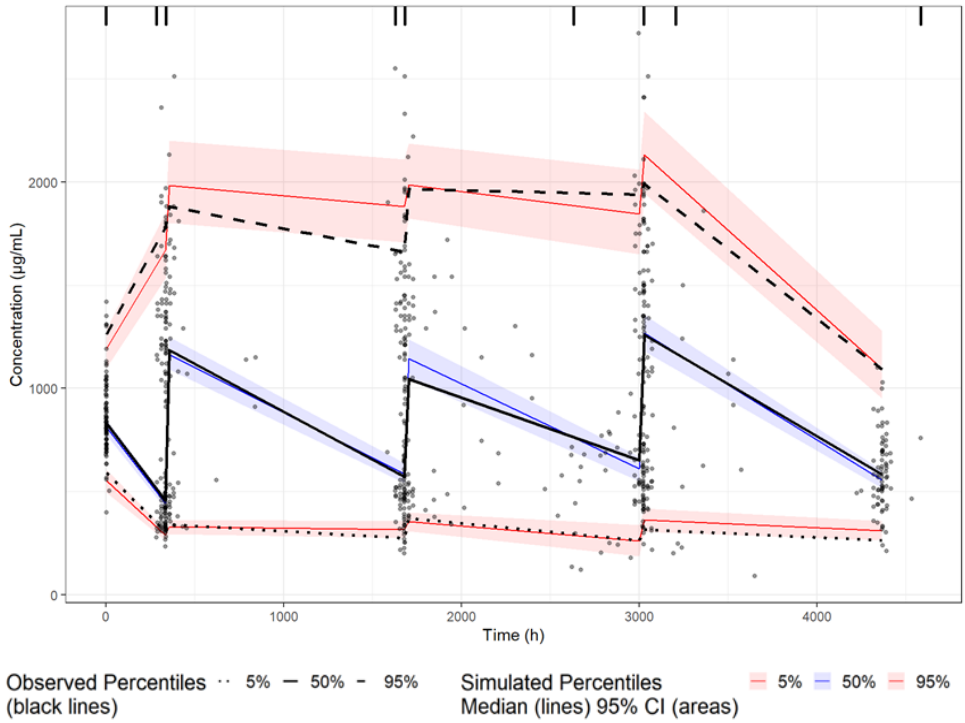
**Figure 2: Final Population-PK Model of Ravulizumab: Goodness-of-Fit**




Note: Thick line on all plots is the LOESS line. Dashed line is the line of identity. Observed and individual/population predicted values are ravulizumab concentrations (µg/mL).
Abbreviations: LOESS = locally weighted scatter-plot smoothing; PK = pharmacokinetic

A pcVPC was used to assess the model performance for describing PK in adult patients with gMG in Study ALXN1210-MG-306 (Figure 3). The observed median, 5th, and 95th percentiles of ravulizumab concentrations were consistent with model predicted values.

**Figure 3: Final Population PK Model of Ravulizumab in Adult Patients with gMG: Prediction-Corrected Visual Predictive Check Semi-log Scale**




Notes: The pcVPC (500 replications) retains the visual interpretation of the traditional VPC while removing the variability that arises from binning across independent variables by normalizing the observed and simulated dependent variable based on the typical population prediction for the median independent variable in the bin.

Abbreviation: CI = confidence interval; gMG = generalized myasthenia gravis; pcVPC = prediction-corrected VPC; PK = pharmacokinetic; VPC = visual predictive check

Final Pop-PK pharmacostatistical parameter estimates for ravulizumab are presented in Table 6.

A sensitivity analysis was performed by using the Pop-PK model developed in patients with PNH as a reference model for assessing which (if any) covariates should be included in the gMG Pop-PK base model. For patients with PNH, the final model included body weight, BMI, sex, and hemoglobin as significant covariates on PK. The PNH model was used to model the current data from Study ALXN1210-MG-306.

**Table 6: Final Population PK Model: Ravulizumab Parameter and Covariate in Adult Patients with gMG**

| Parameter | Estimates[a] | RSE | BSV[b] | Shrinkage |
|---|---|---|---|---|
| **CL (L/h)** | **0.00237** (without PE/PP or IVIg Intervention)<br>0.0108 during IVIg Intervention<br>0.793 during PE/PP Intervention<br>× $(WT/70)^{0.975}$ | 2.89<br>3.92<br>45.5<br><br>8.47 | 18.5%<br>NA<br>NA<br><br>NA | 7.2%<br>NA<br>NA<br><br>NA |
| **Q (L/h)** | **0.0158, Fixed**<br>× $(WT/70)^{0.975}$ | NA<br>8.47 | NA<br>NA | NA<br>NA |
| **Vc (L)** | **2.95**<br>× $(WT/70)^{0.702}$<br>× 0.920 if Female | 2.64<br>6.47<br>2.89 | 9.33%<br>NA<br>NA | 21.0%<br>NA<br>NA |
| **Vp (L)** | **1.94, Fixed** | NA | NA | NA |

| | | | | |
|---|---|---|---|---|
| | × $(WT/70)^{0.702}$ | 6.47 | NA | NA |
| **Error model**<br>Proportional Error (%) | 13.5 | 5.90 | NA | NA |

Note: The reference subject was a 70-kg male patient with gMG.
[a] Parameter estimates are back-transformed from the log-transformed domain. Additional parameter estimates and parameter correlations are presented in gMG Pop-PK-PD Report Section 12.1.
[b] BSV is presented as the standard deviation of the random effect ($\eta_i$), with the % coefficient of variation ($100 \times (\exp(\omega^2)-1)^{0.5}$) in parentheses.
Abbreviations: BSV = between-subject variability; CI = confidence interval; CL = clearance; NA = not applicable; Q = intercompartmental clearance; RSE = relative standard error; Vc = volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment

The covariate effects on CL and Q of ravulizumab are presented below.

- The CL of ravulizumab was dependent on body weight. The exponent for the effect of weight on CL was 0.975 [(Body Weight/70)0.975], suggesting higher CL values in patients with higher body weight. For example, typical subjects with body weight values of 40.0 and 166 kg (corresponding to minimum and maximum values in the PK population; refer to Table 2) are expected to have CL values 42% lower and 2.3-fold (0.00137 and 0.00550 L/h, respectively) relative to a typical subject with a body weight of 70 kg, respectively.
- The CL of ravulizumab during an IVIg intervention was 0.0108 L/h. The effect of IVIg intervention on the CL of ravulizumab was robustly estimated (RSE <5%). The faster CL of ravulizumab during an IVIg intervention corresponded to a t1/2β of 14.7 days.
- The CL of ravulizumab during a PP/PE intervention was 0.793 L/h. The RSE for the effect of PP/PE on CL was high (RSE = 45.5%) since only two patients in the PK population required PP/PE. The faster CL of ravulizumab during a PP/PE intervention corresponded to a t1/2β of 3.6 days.
- The Q of ravulizumab was dependent on body weight. Similar to CL, the exponent for the effect of weight on Q was 0.975 [(Body Weight/70)0.975]. The effect of weight on Q had therefore the same magnitude of effect as that presented for CL.

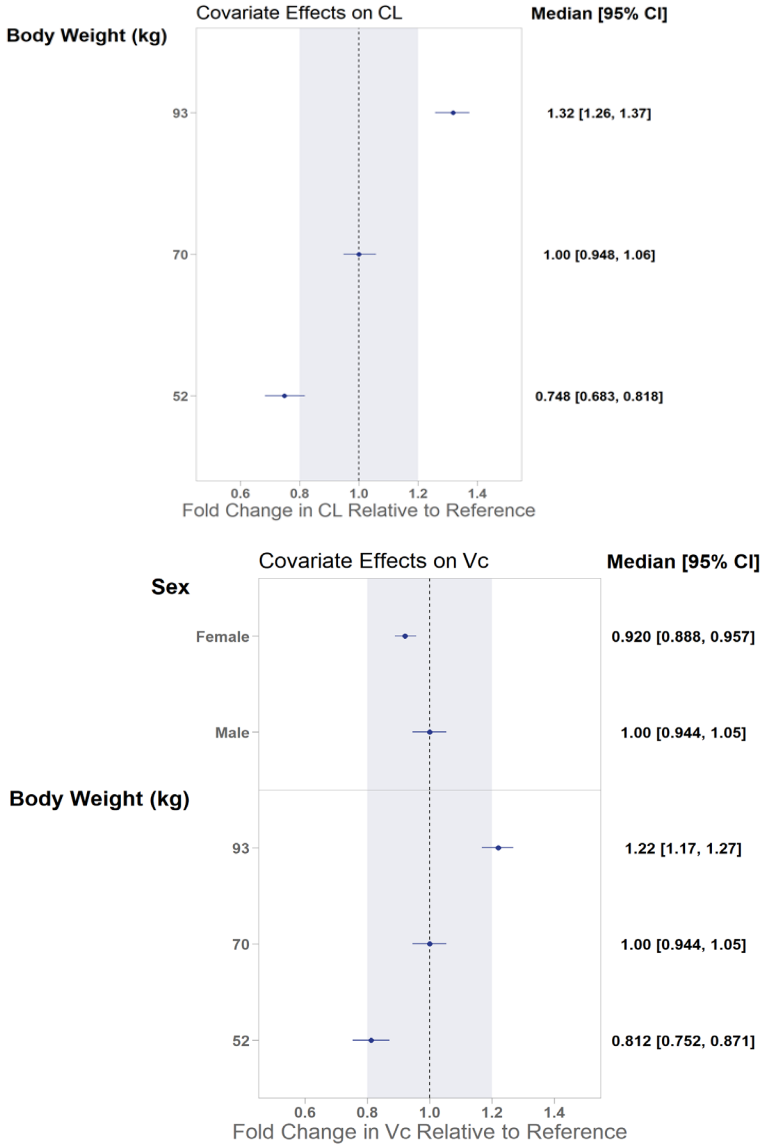
Covariate effects on Vc and Vp of ravulizumab are presented below.

- The Vc of ravulizumab was dependent on body weight. The exponent for the effect of weight on Vc was 0.702 [(Body Weight/70)0.702], suggesting higher Vc values in patients with higher body weight. For example, typical subjects with body weight values of 40.0 and 166 kg (corresponding to minimum and maximum values in the PK population) are expected to have Vc values 32% lower and 1.8-fold higher (1.99 and 5.41 L, respectively) relative to a typical subject with a body weight of 70 kg, respectively.
- Female patients presented a Vc approximately 8% lower than that derived in male patients.
- The Vp of ravulizumab was dependent on body weight and BMI. The effect of weight on Vp had the same magnitude as that presented for Vc.

Summary of Ravulizumab PK parameters in subpopulations of interest

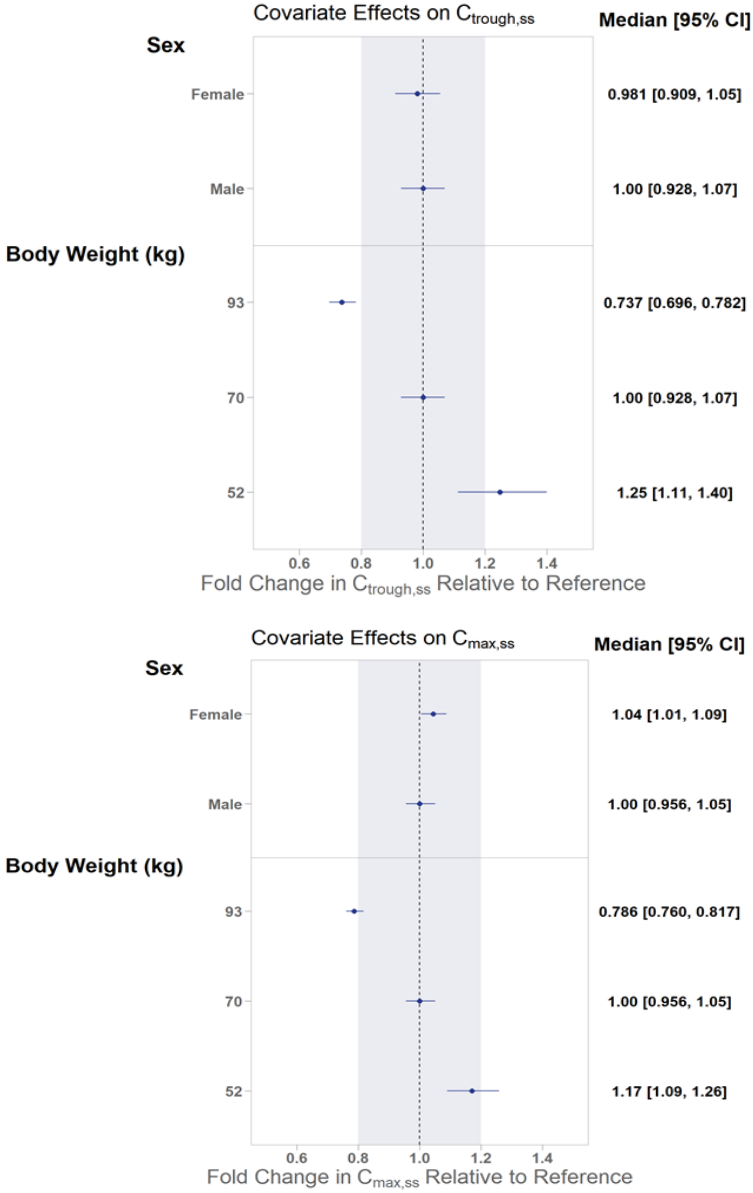
The effect of specific covariates on the CL and Vc of ravulizumab relative to the reference population is presented in Figure 4.

**Figure 4: Forest Plot: Impact of Covariates on the CL and Vc of Ravulizumab**




Note The reference patient was a typical 70-kg male patient with gMG.
Abbreviations: CI = confidence interval; CL = central clearance; gMG = generalized myasthenia gravis; Vc = central volume of distribution

**Figure 5: Forest Plot: Impact of Covariates on the Ctrough,ss and Cmax,ss of Ravulizumab**




Note The reference patient was a typical 70-kg male patient with gMG.
Abbreviations: CI = confidence interval; $C_{max,ss}$ = maximum observed serum concentration under steady-state conditions; $C_{trough,ss}$ = concentration at the end of the dosage interval under steady-state conditions; gMG = generalized myasthenia gravis

Comparison of PK and PD in Patients with PNH, aHUS, or gMG

The PK parameters following body weight-based dosing of ravulizumab IV to patients with PNH, aHUS, or gMG is presented in the table below (Table 7). The ravulizumab exposure parameters in adult patients with gMG are similar to those observed in adult patients with PNH or aHUS.

**Table 7: PK Parameters of Ravulizumab IV Following the Loading Dose and the Last Maintenance Dose During the Primary Evaluation Period for Adult Patients with PNH, aHUS, or gMG**

| PK Parameter (unit) | Dosing Period | Statistic | Adult Patients with PNH | | Adult Patients with aHUS | Adult Patients with gMG |
|---|---|---|---|---|---|---|
| | | | Complement Inhibitor Treatment-Naïve | Eculizumab-Experienced | Complement Inhibitor Treatment-Naïve | Complement Inhibitor Treatment-Naïve |
| $C_{max}$ (µg/mL) | LD | Mean ± SD (CV%); n | 771.4 ± 165.89 (21.5); 125 | 842.9 ± 203.47 (24.1); 96 | 754.3 ± 265.31 (35.2); 52 | 874.1 ± 184.24 (21.1); 86 |
| | Last MD | Mean ± SD (CV%); n | 1378.5 ± 275.94 (20.0); 124 | 1386.3 ± 268.42 (19.4); 95 | 1458.4 ± 256.19 (17.6); 46 | 1548.3 ± 359.43 (23.2); 76 |
| $C_{trough}$ (µg/mL) | LD | Mean ± SD (CV%); n | 391.2 ± 136.77 (35.0); 125 | 405.4 ± 121.24 (29.9); 96 | 313.2 ± 106.16 (33.9); 55 | 417.8 ± 115.51 (27.6); 85 |
| | Last MD | Mean ± SD (CV%); n | 472.7 ± 157.94 (33.4); 124 | 500.8 ± 143.17 (28.6); 95 | 506.9 ± 215.51 (42.5); 46 | 586.6 ± 173.91 (29.6); 70 |

Abbreviations: aHUS = atypical hemolytic uremic syndrome; $C_{max}$ = maximum observed serum concentration; $C_{trough}$ = concentration at the end of the dosing interval; CV = coefficient of variation; gMG = generalized myasthenia gravis; IV = intravenous; LD = loading dose; MD = maintenance dose; PNH = paroxysmal nocturnal hemoglobinuria; SD = standard deviation

The PD following body weight-based dosing of ravulizumab IV to patients with PNH, aHUS, or gMG is similar in that serum free C5 concentration was less than 0.5 µg/mL in 100% of samples obtained during treatment in adult patients with gMG or PNH and in greater than 99.5% of samples in adult patients with aHUS.

## *Immunogenicity*

There were no treatment-emergent ADA-positive findings (ie, positive findings in patients that were not present at baseline or were present at baseline but the titer was higher after study drug administration) after ravulizumab administration during the Randomized-Controlled Period of Study ALXN1210-MG-306. In the ravulizumab group, 8 (9.3%) patients had an ADA-positive sample at baseline (pretreatment) but otherwise had ADA-negative samples at all times post treatment.

A total of 78 (90.7%) patients presented with negative ADA at baseline and 8 (9.3%) presented with confirmed positive ADA at baseline. Baseline ADA did not affect the CL of ravulizumab according to covariate analysis. All post-dose samples were associated with negative ADA in patients who received ravulizumab in the Randomized-Controlled Period.

## *Special populations*

Body weight

A summary of the final Pop-PK model post hoc parameters in adult patients with gMG are shown in Table 8.. The mean (SD) CL and Vc of ravulizumab increased as a function of body weight.

**Table 8 - Summary of Post Hoc PK Parameters for Ravulizumab in Adult Patients with gMG by Body Weight Group**

| Parameters<br>Statistics | ≥ 40 to < 60 kg<br>(N = 7) | ≥ 60 to < 100 kg<br>(N = 47) | ≥ 100 kg<br>(N = 32) | All Patients<br>(N = 86) |
|---|---|---|---|---|
| **CL (L/h)** | | | | |
| Mean (SD) | 0.00182 (0.000429) | 0.00278 (0.000653) | 0.00392 (0.000911) | 0.00313 (0.000996) |
| Median | 0.00191 | 0.00264 | 0.00370 | 0.00303 |
| [2.5th – 97.5th percentile] | [0.00119 – 0.00234] | [0.00203 – 0.00462] | [0.00288 – 0.00633] | [0.00169 – 0.00507] |
| **Q (L/h)** | | | | |
| Mean (SD) | 0.0114 (0.00170) | 0.0183 (0.00245) | 0.0257 (0.00289) | 0.0205 (0.00510) |
| Median | 0.0114 | 0.0181 | 0.0249 | 0.0205 |
| [2.5th – 97.5th percentile] | [0.00923 – 0.0134] | [0.0142 – 0.0221] | [0.0225 – 0.0316] | [0.0105 – 0.0299] |
| **Vc (L)** | | | | |
| Mean (SD) | 2.23 (0.287) | 3.14 (0.462) | 4.09 (0.577) | 3.42 (0.756) |
| Median | 2.31 | 3.04 | 4.06 | 3.44 |
| [2.5th – 97.5th percentile] | [1.82 – 2.55] | [2.34 – 3.93] | [3.21 – 5.45] | [2.20 – 4.84] |
| **Vp (L)** | | | | |
| Mean (SD) | 1.53 (0.166) | 2.16 (0.209) | 2.75 (0.218) | 2.33 (0.423) |
| Median | 1.54 | 2.15 | 2.70 | 2.35 |
| [2.5th – 97.5th percentile] | [1.32 – 1.73] | [1.80 – 2.47] | [2.51 – 3.20] | [1.45 – 3.08] |
| **Vss (L)** | | | | |
| Mean (SD) | 3.76 (0.436) | 5.29 (0.644) | 6.84 (0.764) | 5.74 (1.16) |
| Median | 3.85 | 5.23 | 6.69 | 5.85 |
| [2.5th – 97.5th percentile] | [3.14 – 4.21] | [4.30 – 6.28] | [5.79 – 8.66] | [3.73 – 7.83] |
| **t½ (days)** | | | | |
| Mean (SD) | 63.3 (9.88) | 57.9 (7.85) | 53.1 (7.43) | 56.6 (8.36) |
| Median | 61.6 | 58.3 | 53.5 | 57.2 |
| [2.5th – 97.5th percentile] | [52.2 – 79.9] | [38.5 – 70.8] | [39.8 – 64.8] | [37.8 – 70.9] |

Abbreviations: CL =central clearance; gMG = generalized myasthenia gravis; PK = pharmacokinetic; Q = intercompartmental clearance; t½ = terminal elimination half-life; Vc = central volume of distribution; Vp = peripheral volume of distribution; Vss = volume of distribution at steady state

**Table 9: Descriptive Statistics of Steady State Exposure Parameters of Ravulizumab in Study ALXN1210-MG-306**

| Parameters | ≥40 to < 60 kg<br>(N=7) | ≥60 to < 100 kg<br>(N=47) | ≥100 kg<br>(N=32) | All Patients<br>(N=86) |
|---|---|---|---|---|
| **$C_{trough,ss}$ (µg/mL)** | | | | |
| Mean (SD) | 922 (305) | 635 (160) | 473 (118) | 598 (202) |
| Median | 823 | 625 | 482 | 569 |
| [2.5th – 97.5th percentile] | [625 – 1430] | [305 – 865] | [254 – 667] | [268 – 1060] |
| **$C_{max,ss}$ (µg/mL)** | | | | |
| Mean (SD) | 2280 (485) | 1700 (297) | 1360 (215) | 1620 (382) |
| Median | 2080 | 1750 | 1390 | 1580 |
| [2.5th – 97.5th percentile] | [1860 – 3040] | [1220 – 2230] | [881 – 1770] | [1130 – 2540] |
| **$C_{avg,ss}$ (µg/mL)** | | | | |
| Mean (SD) | 1300 (357) | 925 (193) | 713 (140) | 877 (250) |
| Median | 1170 | 931 | 724 | 834 |
| [2.5th – 97.5th percentile] | [954 – 1880] | [537 – 1210] | [424 – 931] | [494 – 1440] |
| **$AUC_{ss}$ (µg.h/mL)** | | | | |
| Mean (SD) | 1750000 (480000) | 1240000 (260000) | 958000 (188000) | 1180000 (336000) |
| Median | 1570000 | 1250000 | 972000 | 1120000 |
| [2.5th – 97.5th percentile] | [1280000 – 2530000] | [722000 – 1620000] | [569000 – 1250000] | [664000 – 1940000] |

Abbreviations: AUCss = area under the curve over the dosing interval under steady state conditions (ie, 8 weeks); Cavg,ss = average concentrations under steady state conditions; Cmax,ss = maximum concentrations under steady state conditions; Ctrough,ss =minimum concentrations under steady state conditions.
Note: Ravulizumab dosing in patients with body weight ≥ 40 to < 60 kg (2400 mg LD / 3000 mg MD q8w), ≥ 60 to < 100 kg (2700 mg LD / 3300 mg MD q8w), and ≥ 100 kg (3000 mg LD / 3600 mg MD q8w).

Patients with body weight ≥ 40 to < 60 kg treated with a 3000-mg MD q8w presented median Ctrough,ss, Cmax,ss, and Cavg,ss values of approximately 32%, 19%, and 26% higher than patients with body weight ≥ 60 to < 100 kg treated with a 3300-mg MD q8w, respectively.

Patients with body weight ≥ 100 kg treated with a 3600-mg MD q8w presented median Ctrough,ss, Cmax,ss, and Cavg,ss values of 23%, 21%, and 22% lower than patients with body weight ≥ 60 to < 100 kg treated with a 3300-mg MD q8w, respectively.

Japanese vs. non-Japanese patients

**Table 10: Descriptive Statistics of PK and Steady State Exposure Parameters of Ravulizumab in Study ALXN1210-MG-306 – Japanese and Non-Japanese Patients**

| Parameters | Japanese (N=6) | Non-Japanese (N=80) | All Patients (N=86) |
|---|---|---|---|
| **CL (L/h)** | | | |
| Mean (SD) | 0.00231 (0.000471) | 0.00319 (0.000999) | 0.00313 (0.000996) |
| Median [2.5th – 97.5th percentile] | 0.00216 [0.00192 – 0.00308] | 0.00306 [0.00165 – 0.00511] | 0.00303 [0.00169 – 0.00507] |
| **Q (L/h)** | | | |
| Mean (SD) | 0.0155 (0.00393) | 0.0208 (0.00500) | 0.0205 (0.00510) |
| Median [2.5th – 97.5th percentile] | 0.0155 [0.0107 – 0.0214] | 0.0208 [0.0114 – 0.0302] | 0.0205 [0.0105 – 0.0299] |
| **Vc (L)** | | | |
| Mean (SD) | 2.77 (0.595) | 3.46 (0.748) | 3.42 (0.756) |
| Median [2.5th – 97.5th percentile] | 2.59 [2.28 – 3.71] | 3.54 [2.18 – 4.90] | 3.44 [2.20 – 4.84] |
| **Vp (L)** | | | |
| Mean (SD) | 1.91 (0.347) | 2.36 (0.413) | 2.33 (0.423) |
| Median [2.5th – 97.5th percentile] | 1.92 [1.47 – 2.41] | 2.37 [1.54 – 3.10] | 2.35 [1.45 – 3.08] |
| **Vss (L)** | | | |
| Mean (SD) | 4.68 (0.902) | 5.82 (1.14) | 5.74 (1.16) |
| Median [2.5th – 97.5th percentile] | 4.55 [3.76 – 6.11] | 5.90 [3.84 – 7.87] | 5.85 [3.73 – 7.83] |
| **$t_{1/2\beta}$ (days)** | | | |
| Mean (SD) | 60.2 (2.73) | 56.3 (8.58) | 56.6 (8.36) |
| Median [2.5th – 97.5th percentile] | 60.2 [56.8 – 63.1] | 56.7 [37.4 – 71.2] | 57.2 [37.8 – 70.9] |
| **$C_{trough,ss}$ (µg/mL)** | | | |
| Mean (SD) | 735 (112) | 588 (204) | 598 (202) |
| Median [2.5th – 97.5th percentile] | 771 [553 – 829] | 557 [266 – 1090] | 569 [268 – 1060] |
| **$C_{max,ss}$ (µg/mL)** | | | |
| Mean (SD) | 1920 (303) | 1600 (380) | 1620 (382) |
| Median [2.5th – 97.5th percentile] | 2010 [1440 – 2230] | 1530 [1120 – 2590] | 1580 [1130 – 2540] |
| **$C_{avg,ss}$ (µg/mL)** | | | |
| Mean (SD) | 1060 (156) | 863 (251) | 877 (250) |
| Median [2.5th – 97.5th percentile] | 1120 [802 – 1180] | 820 [491 – 1480] | 834 [494 – 1440] |
| **$AUC_{ss}$ (µg.h/mL)** | | | |
| Mean (SD) | 1420000 (210000) | 1160000 (337000) | 1180000 (336000) |
| Median [2.5th – 97.5th percentile] | 1500000 [1080000 – 1590000] | 1100000 [659000 – 1990000] | 1120000 [664000 – 1940000] |

Abbreviations: CL = clearance; Q = intercompartmental clearance; t1/2β = terminal elimination half-life; Vc = volume of distribution in the central compartment; Vp = volume of distribution in the peripheral compartment. Vss = apparent volume of distribution at equilibrium, SD = standard deviation; t1/2□ = terminal elimination half-life; AUCss = area under the curve over the dosing interval under steady state conditions (ie, 8 weeks); Cavg,ss = average concentrations under steady state conditions; Cmax,ss = maximum concentrations under steady state conditions; Ctrough,ss = minimum concentrations under steady state conditions

**Table 11: Descriptive Statistics of Steady State Exposure Parameters of Ravulizumab in Study ALXN1210-MG-306 - Japanese and Non-Japanese Patients by Body Weight Groups**

| Parameters | ≥40 to < 60 kg | | ≥60 to < 100 kg | | ≥100 kg |
|---|---|---|---|---|---|
| | Japanese (N=2) | Non-Japanese (N=5) | Japanese (N=4) | Non-Japanese (N=43) | Non-Japanese (N=32) |
| $C_{trough,ss}$ (µg/mL) | | | | | |
| Mean (SD) | 799 (NA) | 971 (359) | 703 (128) | 629 (162) | 473 (118) |
| Median [2.5th – 97.5th percentile] | 799 [775 – 822] | 840 [619 – 1440] | 723 [546 – 825] | 599 [289 – 866] | 482 [254 – 667] |
| $C_{max,ss}$ (µg/mL) | | | | | |
| Mean (SD) | 2080 (NA) | 2360 (570) | 1830 (355) | 1690 (293) | 1360 (215) |
| Median [2.5th – 97.5th percentile] | 2080 [2080 – 2080] | 2130 [1860 – 3050] | 1850 [1420 – 2220] | 1730 [1220 – 2160] | 1390 [881 – 1770] |
| $C_{avg,ss}$ (µg/mL) | | | | | |
| Mean (SD) | 1160 (NA) | 1360 (421) | 1010 (176) | 917 (195) | 713 (140) |
| Median [2.5th – 97.5th percentile] | 1160 [1150 – 1170] | 1200 [949 – 1890] | 1040 [792 – 1180] | 898 [520 – 1210] | 724 [424 – 931] |
| $AUC_{ss}$ (µg.h/mL) | | | | | |
| Mean (SD) | 1550000 (NA) | 1820000 (566000) | 1360000 (236000) | 1230000 (262000) | 958000 (188000) |
| Median [2.5th – 97.5th percentile] | 1550000 [1540000 – 1570000] | 1620000 [1280000 – 2540000] | 1400000 [1060000 – 1590000] | 1210000 [698000 – 1630000] | 972000 [569000 – 1250000] |

Abbreviations: AUCss = area under the curve over the dosing interval under steady state conditions (ie, 8 weeks); Cavg,ss = average concentrations under steady state conditions; Cmax,ss = maximum concentrations under steady state conditions; Ctrough,ss = minimum concentrations under steady state conditions; NA = not applicable.
Note: a standard deviation was not derived for a sample size less than three.

In Japanese patients ≥40 to < 60 kg, the median Ctrough,ss, Cmax,ss, and Cavg,ss of ravulizumab were 4.9%, 2.3%, and 3.3% lower than those observed in non-Japanese patients, respectively.

In Japanese patients ≥60 to < 100 kg, the median Ctrough,ss, Cmax,ss, and Cavg,ss of ravulizumab were 17.2%, 6.5%, and 13.7% higher than those observed in non-Japanese patients, respectively.

## 2.3.3. Pharmacodynamics

### *Mechanism of action*

Ravulizumab is a humanized monoclonal antibody that binds to 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.

Autoantibodies recognize targeted neural or muscle tissues, including the acetylcholine receptor (AChR), leading to uncontrolled terminal complement activation at the neural or muscle surface[20]. Autoantibody-driven uncontrolled terminal complement activation with membrane attack complex (MAC)-dependent lysis and activation, and C5a-dependent inflammation at the neuromuscular junction (NMJ) causes AChR loss and failure of neuromuscular transmission.

[20] Ha, J. C., & Richman, D. P. (2015). Myasthenia gravis and related disorders: Pathology and molecular pathogenesis. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1852(4), 651-657.

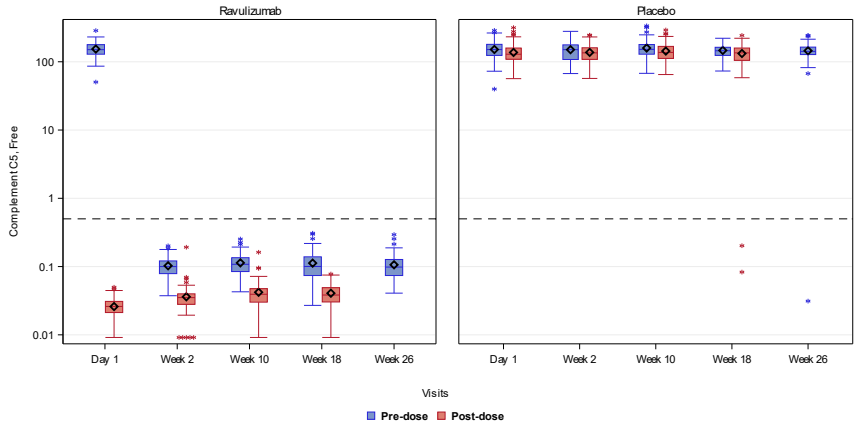
Consistent with this model, both complement component (C) 3 (C3a and C3b) fragments and the MAC C5b-9 have been found in NMJs of MG patients[21] . Taken together, the data support that uncontrolled terminal complement activation at the NMJ plays a role in the destruction of post-synaptic structure. Rapid, complete, and sustained inhibition of terminal complement activation is a biologically rational approach to prevent the damage caused in patients with gMG.

## 2.3.4. PK/PD modelling

Exposure-efficacy relationship

All serum free C5 concentrations post dose for the ravulizumab-treated patients during the Randomized-Controlled Period were < 0.5 µg/mL (Figure ), including patients experiencing clinical deterioration. Thus, ravulizumab treatment resulted in immediate, complete, and sustained terminal complement inhibition in all patients with gMG throughout the entire treatment period with body weight-based dosing.

**Figure 6: Serum Free C5 Concentration-Time Profiles (Study ALXN1210-MG-306 Full Analysis Set)**




Note: For serum free C5 concentrations that were BLQ, LLOQ/2 = 0.00915 µg/mL was utilized. Y-axis is presented on a log scale. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean, and the top and the bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers represent the 1.5 IQR of the lower quartile and upper quartile. Outliers are represented by asterisk beyond the whiskers. Dashed horizontal line indicates serum free C5 concentration of 0.5 µg/mL. Only data from scheduled visits were included in this figure.

Abbreviations: BLQ = below the limit of quantification; C5 = complement component 5; IQR = interquartile range; LLOQ = lower limit of quantification

[21] Sahashi K, Engel AG, Linstrom JM, Lambert EH, Lennon VA. Ultrastructural localization of immune complexes (IgG and C3) at the end-plate in experimental autoimmune myasthenia gravis. J Neuropathol Exp Neurol. 1978;37(2):212-223.

Exposure-safety analysis

**Table 12: Summary of Adverse Events Occurring in Greater Than or Equal to 5% of Ravulizumab-treated Patients During the Randomized-Controlled Period of Study ALXN1210-MG-306**

| Adverse Event | Frequency | Percent (%)[a] |
|---|---|---|
| Any adverse event | 78 | 90.7 |
| Headache | 16 | 18.6 |
| Diarrhoea | 13 | 15.1 |
| Nausea | 9 | 10.5 |
| Dizziness | 8 | 9.3 |
| Back pain | 7 | 8.1 |
| Arthralgia | 6 | 7.0 |
| Fatigue | 6 | 7.0 |
| Abdominal pain | 5 | 5.8 |
| COVID-19 | 5 | 5.8 |
| Urinary tract infection | 5 | 5.8 |

[a] The percentage is derived based on 86 patients who received ravulizumab treatment during the Randomized-Controlled Period of Study ALXN1210-MG-306.

The probability of an AE observed as a function of model-predicted $C_{max,ss}$ of ravulizumab is presented by $C_{max,ss}$ quartiles in Table 13 and as a function of model-predicted $AUC_{ss}$ by $AUC_{ss}$ quartiles in Table 14.

Similar results were observed for the $C_{trough,ss}$ and $C_{avg,ss}$ of ravulizumab).

**Table 13: Probability of Adverse Events as a Function of Model-Predicted Ravulizumab Maximum Concentration at Steady State by Quartile in Study ALXN1210-MG-306**

| **Adverse Event Statistic** | **Q1 of $C_{max,ss}$ (874 – 1372 µg/mL) (N = 22)** | **Q2 of $C_{max,ss}$ (1383 – 1572 µg/mL) (N = 21)** | **Q3 of $C_{max,ss}$ (1586 – 1838 µg/mL) (N = 21)** | **Q4 of $C_{max,ss}$ (1860 – 3072 µg/mL) (N = 22)** | **Overall (N = 86)** |
|---|---|---|---|---|---|
| **Any adverse event** | | | | | |
| n (%)<br>[95% CI] | 21 (95.5)<br>[77.2 – 99.9] | 19 (90.5)<br>[69.6 – 98.8] | 19 (90.5)<br>[69.6 – 98.8] | 19 (86.4)<br>[65.1 – 97.1] | 78 (90.7)<br>[82.5 – 95.9] |
| **Headache** | | | | | |
| n (%)<br>[95% CI] | 2 (9.1)<br>[1.1 – 29.2] | 5 (23.8)<br>[8.2 – 47.2] | 4 (19.9)<br>[5.4 – 41.9] | 5 (22.7)<br>[7.8 – 45.4] | 16 (18.6)<br>[11.0 – 28.4] |
| **Diarrhoea** | | | | | |
| n (%)<br>[95% CI] | 6 (27.3)<br>[10.7 – 50.2] | 0<br>[0.0 – 16.1] | 3 (14.3)<br>[3.0 – 36.3] | 4 (18.2)<br>[5.2 – 40.3] | 13 (15.1)<br>[8.3 – 24.5] |
| **Nausea** | | | | | |
| n (%)<br>[95% CI] | 1 (4.5)<br>[0.1 – 22.8] | 4 (19.0)<br>[5.4 – 41.9] | 2 (9.5)<br>[1.2 – 30.4] | 2 (9.1)<br>[1.1 – 29.2] | 9 (10.5)<br>[4.9 – 18.9] |
| **Dizziness** | | | | | |
| n (%)<br>[95% CI] | 2 (9.1)<br>[1.1 – 29.2] | 3 (14.3)<br>[3.0 – 36.3] | 1 (4.8)<br>[0.1 – 23.8] | 2 (9.1)<br>[1.1 – 29.2] | 8 (9.3)<br>[4.1 – 17.5] |
| **Back pain** | | | | | |
| n (%)<br>[95% CI] | 1 (4.5)<br>[0.1 – 22.8] | 2 (9.5)<br>[1.2 – 30.4] | 2 (9.5)<br>[1.2 – 30.4] | 2 (9.1)<br>[1.1 – 29.2] | 7 (8.1)<br>[3.3 – 16.1] |
| **Arthralgia** | | | | | |

**Table 13: Probability of Adverse Events as a Function of Model-Predicted Ravulizumab Maximum Concentration at Steady State by Quartile in Study ALXN1210-MG-306**

| Adverse Event Statistic | Q1 of $C_{max,ss}$ (874 – 1372 µg/mL) (N = 22) | Q2 of $C_{max,ss}$ (1383 – 1572 µg/mL) (N = 21) | Q3 of $C_{max,ss}$ (1586 – 1838 µg/mL) (N = 21) | Q4 of $C_{max,ss}$ (1860 – 3072 µg/mL) (N = 22) | Overall (N = 86) |
|---|---|---|---|---|---|
| n (%)<br>[95% CI] | 0<br>[0.0 – 15.4] | 1 (4.8)<br>[0.1 – 23.8] | 2 (9.5)<br>[1.2 – 30.4] | 3 (13.6)<br>[2.9 – 34.9] | 6 (7.0)<br>[2.6 – 14.6] |
| **Fatigue** | | | | | |
| n (%)<br>[95% CI] | 2 (9.1)<br>[1.1 – 29.2] | 3 (14.3)<br>[3.0 – 36.3] | 1 (4.8)<br>[0.1 – 23.8] | 0<br>[0.0 – 15.4] | 6 (7.0)<br>[2.6 – 14.6] |
| **Abdominal pain** | | | | | |
| n (%)<br>[95% CI] | 2 (9.1)<br>[1.1 – 29.2] | 0<br>[0.0 – 16.1] | 3 (14.3)<br>[3.0 – 36.3] | 0<br>[0.0 – 15.4] | 5 (5.8)<br>[1.9 – 13.0] |
| **COVID-19** | | | | | |
| n (%)<br>[95% CI] | 1 (4.5)<br>[0.1 – 22.8] | 3 (14.3)<br>[3.0 – 36.3] | 0<br>[0.0 – 16.1] | 1 (4.5)<br>[0.1 – 22.8] | 5 (5.8)<br>[1.9 – 13.0] |
| **Urinary tract infection** | | | | | |
| n (%)<br>[95% CI] | 0<br>[0.0 – 15.4] | 2 (9.5)<br>[1.2 – 30.4] | 1 (4.8)<br>[0.1 – 23.8] | 2 (9.1)<br>[1.1 – 29.2] | 5 (5.8)<br>[1.9 – 13.0] |

Note: 95% CI are calculated using the Clopper and Pearson method. Adverse events that occurred in ≥ 5% of ravulizumab-treated patients during the Randomized-Controlled Period of Study ALXN-MG-306 are included.

Abbreviations: CI = confidence interval; $C_{max,ss}$ = maximum observed serum concentration under steady-state conditions; Q1 = 1st quartile; Q2 = 2nd quartile; Q3 = 3rd quartile; Q4 = 4th quartile

**Table 14: Probability of Adverse Events as a Function of Model-Predicted Ravulizumab Area Under the Concentration-Time Curve at Steady State by Quartile in Study ALXN1210-MG-306**

| Adverse Event Statistic | Q1 of $AUC_{ss}$ (525660 – 971458 µg × h/mL) (N = 22) | Q2 of $AUC_{ss}$ (973510 – 1116088 µg × h/mL) (N = 21) | Q3 of $AUC_{ss}$ (1125641 – 1359394 µg × h/mL) (N = 21) | Q4 of $AUC_{ss}$ (1379040 – 2573600 µg × h/mL) (N = 22) | Overall (N = 86) |
|---|---|---|---|---|---|
| **Any adverse event** | | | | | |
| n (%)<br>[95% CI] | 21 (95.5)<br>[77.2 – 99.9] | 19 (90.5)<br>[69.6 – 98.8] | 19 (90.5)<br>[69.6 – 98.8] | 19 (86.4)<br>[65.1 – 97.1] | 78 (90.7)<br>[82.5 – 95.9] |
| **Headache** | | | | | |
| n (%)<br>[95% CI] | 3 (13.6)<br>[2.9 – 34.9] | 3 (14.3)<br>[3.0 – 36.3] | 5 (23.8)<br>[8.2 – 47.2] | 5 (22.7)<br>[7.8 – 45.4] | 16 (18.6)<br>[11.0 – 28.4] |
| **Diarrhoea** | | | | | |
| n (%)<br>[95% CI] | 5 (22.7)<br>[7.8 – 45.4] | 1 (4.8)<br>[0.1 – 23.8] | 4 (19.0)<br>[5.4 – 41.9] | 3 (13.6)<br>[2.9 – 34.9] | 13 (15.1)<br>[8.3 – 24.5] |
| **Nausea** | | | | | |
| n (%)<br>[95% CI] | 5 (22.7)<br>[7.8 – 45.4] | 1 (4.8)<br>[0.1 – 23.8] | 1 (4.8)<br>[0.1 – 23.8] | 2 (9.1)<br>[1.1 – 29.2] | 9 (10.5)<br>[4.9 – 18.9] |
| **Dizziness** | | | | | |
| n (%)<br>[95% CI] | 2 (9.1)<br>[1.1 – 29.2] | 4 (19.0)<br>[5.4 – 41.9] | 0<br>[0.0 – 16.1] | 2 (9.1)<br>[1.1 – 29.2] | 8 (9.3)<br>[4.1 – 17.5] |
| **Back pain** | | | | | |
| n (%)<br>[95% CI] | 1 (4.5)<br>[0.1 – 22.8] | 1 (4.8)<br>[0.1 – 23.8] | 4 (19.0)<br>[5.4 – 41.9] | 1 (4.5)<br>[0.1 – 22.8] | 7 (8.1)<br>[3.3 – 16.1] |
| **Arthralgia** | | | | | |

**Table 14: Probability of Adverse Events as a Function of Model-Predicted Ravulizumab Area Under the Concentration-Time Curve at Steady State by Quartile in Study ALXN1210-MG-306**

| Adverse Event Statistic | Q1 of $AUC_{ss}$ (525660 – 971458 µg × h/mL) (N = 22) | Q2 of $AUC_{ss}$ (973510 – 1116088 µg × h/mL) (N = 21) | Q3 of $AUC_{ss}$ (1125641 – 1359394 µg × h/mL) (N = 21) | Q4 of $AUC_{ss}$ (1379040 – 2573600 µg × h/mL) (N = 22) | Overall (N = 86) |
|---|---|---|---|---|---|
| n (%) [95% CI] | 0 [0.0 – 15.4] | 1 (4.8) [0.1 – 23.8] | 2 (9.5) [1.2 – 30.4] | 3 (13.6) [2.9 – 34.9] | 6 (7.0) [2.6 – 14.6] |
| **Fatigue** | | | | | |
| n (%) [95% CI] | 2 (9.1) [1.1 – 29.2] | 4 (19.0) [5.4 – 41.9] | 0 [0.0 – 16.1] | 0 [0.0 – 15.4] | 6 (7.0) [2.6 – 14.6] |
| **Abdominal pain** | | | | | |
| n (%) [95% CI] | 1 (4.5) [0.1 – 22.8] | 1 (4.8) [0.1 – 23.8] | 2 (9.5) [1.2 – 30.4] | 1 (4.5) [0.1 – 22.8] | 5 (5.8) [1.9 – 13.0] |
| **COVID-19** | | | | | |
| n (%) [95% CI] | 2 (9.1) [1.1 – 29.2] | 2 (9.5) [1.2 – 30.4] | 0 [0.0 – 16.1] | 1 (4.5) [0.1 – 22.8] | 5 (5.8) [1.9 – 13.0] |
| **Urinary tract infection** | | | | | |
| n (%) [95% CI] | 1 (4.5) [0.1 – 22.8] | 1 (4.8) [0.1 – 23.8] | 1 (4.8) [0.1 – 23.8] | 2 (9.1) [1.1 – 29.2] | 5 (5.8) [1.9 – 13.0] |

Note: 95% CI are calculated using the Clopper and Pearson method. Adverse events that occurred in ≥ 5% of ravulizumab-treated patients during the Randomized-Controlled Period of Study ALXN-MG-306 are included.
Abbreviations: $AUC_{ss}$ = area under the serum concentration-time curve at steady state; CI = confidence interval; Q1 = 1st quartile; Q2 = 2nd quartile; Q3 = 3rd quartile; Q4 = 4th quartile

## 2.3.5. Discussion on clinical pharmacology

The clinical pharmacology properties of ravulizumab in patients with gMG has been characterized using experimental information from Study ALXN1210-MG-306, which included pharmacokinetic and pharmacodynamic observations in 86 patients receiving ravulizumab and 89 patients in the placebo group. The model development programs were considered adequate by CHMP.

Ravulizumab Cmax and Ctrough concentrations were remarkably lower in the highest (above 100 kg) weight group compared to the lowest one (40-60 kg) even after the first (loading) dose. This difference became much more pronounced through the last maintenance dose, reaching a difference of 47% in Ctrough between the highest and the lowest bodyweight groups.

The population PK model used incorporates a two-compartment model with linear clearance that was previously developed in healthy subjects and patients with PNH. In general, the structural and stochastic elements of the population PK model are adequate to properly describe the observed data in patients with gMG. PK parameters of the peripheral compartment (Q and Vp) were fixed to the value obtained in patients with PNH and healthy subjects, but CL, Vc and covariates effects were re-estimated in patients with gMG. This modelling strategy might be explained by the lack of sufficient data in the alpha- and beta-distribution phases. However, the assumption that similar Vp and Q across the different indications is unclear and it may cause a model-misspecification on other PK parameters of the model. Despite of this, the relative standard errors of PK parameters were below 10%, except for IVIg intervention (due to the unbalanced and scarce (n=2) distribution of subjects), showing the adequacy of the final parameter estimates.

A sensitivity analysis was performed by using the Pop-PK model developed in patients with PNH as a reference model for assessing which (if any) covariates should be included in the gMG Pop-PK base model. For patients with PNH, the final model included body weight, BMI, sex, and hemoglobin as

significant covariates on PK. It was noted that, the effect of hemoglobin on CL and Vc were not statistically significant because the 95% CI included 0. The effect of BMI on Vc and Vp remained statistically significant. The effect of sex on Vc was also statistically significant. Overall, the effect of hemoglobin originally identified in patients with PNH was no longer significant in patients with gMG.

Comparison of exposure in patients with PNH, aHUS and gMG showed similar exposure PK metrics and half-life of ravulizumab, suggesting no significant differences due to disease condition.

Regarding assessment of immunogenicity, there were no treatment-emergent ADA-positive findings and as such no impact of immunogenicity on ravulizumab PK or PD is expected in patients with gMG.

Of note, the covariate analysis revealed a clinically relevant effect of body weight on Ctrough,ss and Cmax,ss, suggesting that differences >20% are expected in patients with body weight <52 and >93 kg compared to the reference patient (70 kg). Despite the fact that experimental ravulizumab PK exposure metrics following the maintenance dose are different to model-predicted ravulizumab PK exposure metrics following the maintenance dose, both suggest clear differences in exposure despite the different dosing regimen by body weight group. From the PK/PD relationship no clinically relevant differences in biomarker response and safety events among the three body-weight sub-groups of adult patients have been identified and the dosing regimen recommended in patients with gMG is identical to the one proposed in patients with PNH or aHUS. This is considered adequate by the CHMP.

Regarding the clinical evaluation of the effect of ravulizumab in Japanese and non-Japanese patients no relevant differences in exposure were observed. However, since only six Japanese patients were enrolled no definitive conclusions can be made at this time.

The PK/PD relationship has been empirically established through the graphical representation of experimental PK and PD observations, but no model-based approach has been conducted that would enable to understand whether alternative dosing strategies might be of interest. Based on the experimental evidence, the selection of 175 µg/mL might be justified based on C5 free concentration in treated patients vs. placebo arm. This result is in line with the threshold identified for patients with PNH and aHUS. Free C5 concentrations in the ravulizumab group were definitely below this threshold not only post-dose, but also pre-dose, even the outliers. It was further clarified that these low free C5 values were bioanalytical outliers most likely, since no assignable cause of these low free C5 values were revealed by the bioanalytical run data and subsequent sample analysis report and ravulizumab concentrations of these patients were always below the level of quantification, justifying that they were not exposed inadvertently to ravulizumab during the study.

The exposure-safety evaluation revealed no clinically relevant relationship of ravulizumab quartiles and the incidence/probability of adverse events. A minor trend was observed for arthralgia, headache and nausea, but in general the probability were below 25%. Therefore, no significant exposure-safety relationship in patients with gMG is observed in Study ALXN1210-MG-306.

## 2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology properties of ravulizumab in patients with gMG have been characterized in 86 patients receiving ravulizumab and 89 subjects receiving placebo (Study ALXN1210-MG-306). The modelling strategy and study design conditions seem appropriate to achieve the planned objectives. A previously developed population PK model in patients with PNH has been applied, showing its ability to characterize the observed data.

The available clinical pharmacology data submitted supports the use of ravulizumab in the approved indication.

## *2.4. Clinical efficacy*

### 2.4.1. Dose response study

The ravulizumab dosing regimen was designed based on modelling and simulation analyses using data from healthy subjects and patients with PNH and aHUS to maintain efficacious concentrations across the longer dosing interval.

The body weight-based ravulizumab treatment regimen proposed for adult patients with gMG is identical to the one approved for PNH and aHUS which includes a loading dose on Day 1, followed by maintenance doses on Day 15 and every 8 weeks (q8w) thereafter, administered by IV infusion (Table 15 ).

**Table 15 : Ravulizumab Weight-Based Dosing Regimen**

| Body Weight | Loading Dose (mg) | Maintenance Dose (mg) |
|---|---|---|
| ≥ 40 to < 60 kg | 2400 | 3000 |
| ≥ 60 to < 100 kg | 2700 | 3300 |
| ≥ 100 kg | 3000 | 3600 |

Plasma exchange (PE), plasmapheresis (PP), and intravenous immunoglobulin (IVIg) have been shown to reduce ravulizumab serum levels Information on Supplemental Doses after PE, PP or IVIg are shown in Table 16.

**Table 16: Supplemental Doses after PE, PP or IVIg**

| Body Weight (kg) | Most Recent Dose (mg) | Supplemental Dose (mg) following each PP or PE session | Supplemental Dose (mg) following course of IVIg |
|---|---|---|---|
| ≥ 40 to < 60 kg | 2400 | 1200 | 600 |
| | 3000 | 1500 | |
| ≥ 40 to < 60 kg | 2700 | 1500 | 600 |
| | 3300 | 1800 | |
| ≥ 100 kg | 3000 | 1500 | 600 |
| | 3600 | 1800 | |

Abbreviations: IVIg = intravenous immunoglobulin; PE = plasma exchange; PP = plasmapheresis.

The dose recommendations by body weight are justified based on differences in exposure that ensure serum free complement component complete inhibition (see tables 17 and 18).

**Table 17: Ravulizumab PK Parameters Following the First (Loading) Dose (Study ALXN1210-MG-306 PK Analysis Set)**

| Parameter | Statistics | All Patients | ≥ 40 to < 60 kg | ≥ 60 to < 100 kg | ≥ 100 kg |
|---|---|---|---|---|---|
| $C_{max}$ (µg/mL) | n | 86 | 7 | 47 | 32 |
| | Mean (SD) | 874.1 (184.24) | 1054.3 (163.57) | 912.1 (170.39) | 778.8 (160.96) |
| | CV% | 21.1 | 15.5 | 18.7 | 20.7 |
| | Median (min, max) | 836.0 (399, 1420) | 1060.0 (778, 1310) | 868.0 (692, 1420) | 779.5 (399, 1350) |
| $C_{trough}$ (µg/mL) | n | 85 | 7 | 46 | 32 |
| | Mean (SD) | 417.8 (115.51) | 555.7 (116.45) | 438.5 (118.11) | 357.8 (68.12) |
| | CV% | 27.6 | 21.0 | 26.9 | 19.0 |
| | Median (min, max) | 397.0 (234, 1000) | 520.0 (451, 751) | 422.0 (305, 1000) | 339.0 (234, 570) |

| Parameter | Statistics | All Patients | ≥ 40 to < 60 kg | ≥ 60 to < 100 kg | ≥ 100 kg |
|---|---|---|---|---|---|

Abbreviations: Cmax = maximum observed serum concentration; Ctrough = concentration at the end of the dosage interval; CV = coefficient of variation; max = maximum; min = minimum; PK = pharmacokinetics; SD = standard deviation

**Table 18: Ravulizumab PK Parameters Following the Final Maintenance Dose (Study ALXN1210-MG-306 PK Analysis Set**

| Parameter | Statistics | All Patients | ≥ 40 to < 60 kg | ≥ 60 to < 100 kg | ≥ 100 kg |
|---|---|---|---|---|---|
| $C_{max}$ (µg/mL) | n | 76 | 4 | 43 | 29 |
| | Mean (SD) | 1548.3 (359.43) | 2015.0 (345.40) | 1645.3 (337.63) | 1340.1 (267.95) |
| | CV% | 23.2 | 17.1 | 20.5 | 20.0 |
| | Median (min, max) | 1500.0 (810, 2510) | 1900.0 (1750, 2510) | 1660.0 (1060, 2410) | 1340.0 (810, 1990) |
| $C_{trough}$ (µg/mL) | n | 70 | 4 | 39 | 27 |
| | Mean (SD) | 586.6 (173.91) | 887.3 (82.72) | 635.7 (157.28) | 471.3 (109.47) |
| | CV% | 29.6 | 9.3 | 24.7 | 23.2 |
| | Median (min, max) | 570.0 (211, 1030) | 866.5 (817, 999) | 649.0 (241, 1030) | 456.0 (211, 635) |

Note: Data were excluded for patients after they received a supplemental dose following PE, PP, or IVIg.
Abbreviations: Cmax = maximum observed serum concentration; Ctrough = concentration at the end of the dosage interval; CV = coefficient of variation; IVIg = intravenous immunoglobulin; max = maximum; min = minimum; PE = plasma exchange; PK = pharmacokinetics; PP = plasmapheresis; SD = standard deviation

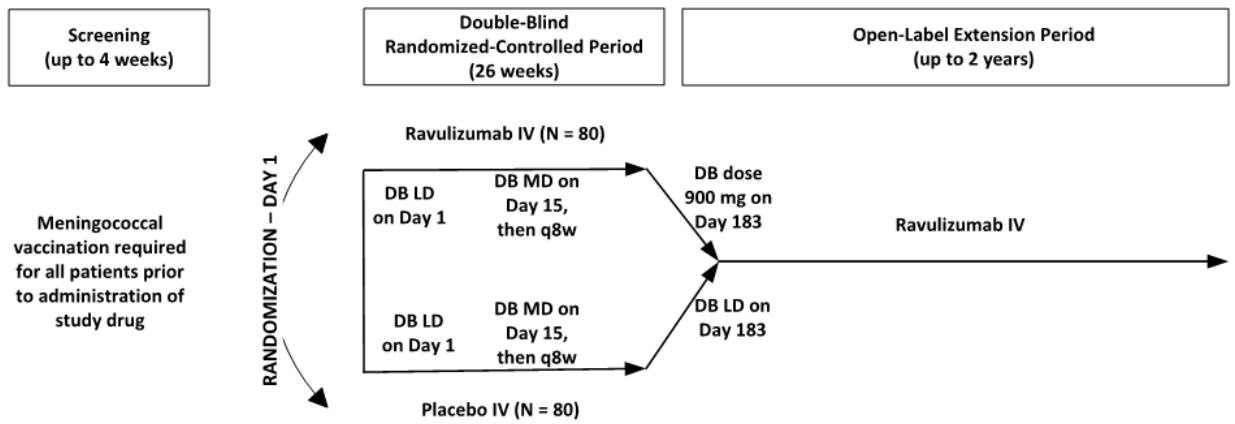
## 2.4.2. Main study

### *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 Myasthenia Gravis*

Study ALXN1210 MG 306 is a Phase 3, randomized, double-blind, parallel-group, placebo controlled, multicenter study with an ongoing open-label extension to evaluate the safety and efficacy of ravulizumab administered by IV infusion for the treatment of adult patients with gMG.

The study consists of an up to 4 week Screening Period, a 26 week double-blind, Randomized Controlled Period, and an Open-Label Extension Period of up to 2 years (Figure 8).

**Figure 8: Study Design Schematic for Study ALXN1210-MG-306**



Abbreviations: DB = double-blind; IV = intravenous; LD = loading dose; MD = maintenance dose.

## *Methods*

## Study participants

Enrolled in this study were male and female patients ≥ 18 years of age (at the time of informed consent) diagnosed with gMG (at least 6 months prior to the Screening Visit) confirmed by positive serologic test for anti-AChR antibodies.

With respect to the type of Patient and Disease Characteristics the main following criteria were required

1. Diagnosed with MG at least 6 months (180 days) prior to the date of the Screening Visit

2. Confirmation of eligibility by:

    a. Positive serologic test for anti-AChR Abs as confirmed at screening, and

    b. One of the following (either historical or during screening):

        - abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation
        - positive anticholinesterase test (eg, edrophonium chloride test)
        - demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating physician

3. Myasthenia Gravis Foundation of America Clinical Classification Class II to IV at screening

4. MG-ADL profile must be ≥ 6 at screening and randomization (Day 1)

5. Patients receiving treatment with any of the following must have been receiving treatment and on a stable dose for the time periods specified below prior to the date of the Screening Visit:

- Azathioprine (AZA): Must have been on AZA for ≥ 6 months (180 days) and have been on a stable dose for ≥ 2 months (60 days)
- Immunosuppressive therapies (ie, mycophenolate mofetil [MMF], methotrexate [MTX], cyclosporine [CYC], tacrolimus [TAC], or cyclophosphamide [CY]), must have been on the IST for ≥ 3 months (90 days) and have been on a stable dose for ≥ 1 month (30 days)
- Oral corticosteroids, must have been on a stable dose for ≥4 weeks (28 days)
- A cholinesterase inhibitor, at the time of the Screening Visit, must have been on a stable dose for ≥ 2 weeks (14 days)

6. All patients must be vaccinated against meningococcal infections within the 3 years prior to, or at the time of, initiating study drug.

7. Body weight ≥ 40 kg at the time of screening

Patients were excluded from the study if they had any active or untreated thymoma or history of thymic carcinoma or thymic malignancy; history of thymectomy, thymomectomy, or any thymic surgery within the 12 months prior to screening; clinical features that are consistent with myasthenia gravis

crisis/exacerbation or Clinical Deterioration at the time of the Screening Visit, or at any time prior to randomization; or previous treatment with complement inhibitors.

## Treatments

During the Randomized-Controlled Period, patients received a weight-based loading dose of ravulizumab (Table 19) or placebo on Day 1 followed by blinded maintenance doses of ravulizumab or placebo on Day 15 and then once every 8 weeks (q8w) thereafter. Both ravulizumab and placebo were administered by IV infusion.

**Table 19: Ravulizumab Dosing Regimen for the Randomized-Controlled Period**

| Body Weight | Loading Dose (Day 1) | Maintenance Dose (Day 15; administered q8w) |
|---|---|---|
| ≥ 40 to < 60 kg | 2400 mg | 3000 mg |
| ≥ 60 to < 100 kg | 2700 mg | 3300 mg |
| ≥ 100 kg | 3000 mg | 3600 mg |

Abbreviation: q8w = every 8 weeks

Following completion of the Day 183 (Week 26) assessments, in order to maintain the blind of the Randomized-Controlled Period, patients in the placebo group received a blinded loading dose of ravulizumab (2400 mg for those weighing ≥ 40 to < 60 kg, 2700 mg for those weighing ≥ 60 to < 100 kg, or 3000 mg for those weighing ≥ 100 kg). Patients in the ravulizumab group received a blinded ravulizumab dose of 900 mg starting at Week 28, all patients began open-label ravulizumab maintenance dosing q8w.

Throughout the study, rescue therapy (eg, high-dose corticosteroid, PE/PP, or IVIg) was allowed if a patient experienced protocol-defined Clinical Deterioration. For this protocol, Clinical Deterioration is defined as any of the following:

1. Patients who experience an MG Crisis, which is defined as weakness from MG that is severe enough to necessitate intubation or to delay extubation following surgery. The respiratory failure is due to weakness of respiratory muscles. Severe bulbar (oropharyngeal) muscle weakness often accompanies the respiratory muscle weakness, or may be the predominant feature in some patients; or,

2. Significant symptomatic worsening to a score of 3 or a 2-point worsening from Baseline on any one of the individual MG-Activities of Daily Living (MG-ADL) items other than double vision or eyelid droop; or,

3. Administration of rescue therapy to a patient whose, in the opinion of the Investigator or Investigator-designated physician, health would be in jeopardy, if rescue therapy were not given (eg, emergent situations).

During the OLE period, all patients from investigative sites in the concerned countries will switch from the 10 mg/mL to the 100 mg/mL formulation of ravulizumab with no change to the weight-based dose regimen until end of the study (Section 4.5). Following the formulation change, all subsequent ravulizumab doses will use the 100 mg/mL formulation

## Objectives

*Primary*

To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in the MG-ADL profile

*Secondary*

To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in the QMG total score.

To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in quality of life measures.

To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on other efficacy endpoints.

*Exploratory*

To assess the efficacy of ravulizumab in the treatment of gMG based on other efficacy endpoints throughout the study.

*PK/PD/Immunogenicity*

To evaluate the PK/PD and immunogenicity of ravulizumab in the treatment of gMG throughout the study.

*Safety*

To characterize the overall safety of ravulizumab in the treatment of gMG.

## Outcomes/endpoints

*Primary*

Change from Baseline in MG-ADL total score at Week 26 of the Randomized-Controlled Period.

*Secondary*

- Change from Baseline in QMG total score at Week 26.
- Improvement of at least 5 points in the QMG total score from Baseline at Week 26.
- Change from Baseline in the MG-QoL15r score at Week 26.
- Change from Baseline in Neuro-QoL Fatigue score at Week 26.
- Improvement of at least 3 points in the MG-ADL total score from Baseline at Week 26.

*Exploratory*

- Change from Baseline in the MGC score at Week 26.
- MGFA PIS at Week 26
- Change from Baseline in EQ 5D 5L at Week 26.
- Change from Baseline in MG-ADL subcomponent scores (bulbar, limbs, respiratory, and ocular) at Week 26.
- Change from Baseline in QMG subcomponent scores (bulbar, limbs, respiratory, and ocular) at Week 26.
- Incidence of hospitalizations/MG-related hospitalizations.

- Incidence of Clinical Deterioration/MG crisis.

*PK/PD/Immunogenicity*

- Change in serum ravulizumab concentration over time.
- Change in serum free C5 concentration over time.
- Incidence of treatment-emergent antidrug antibodies over time

*Safety*

- Incidence of adverse events and serious adverse events over time.
- Changes from Baseline in vital signs and laboratory assessments

## Sample size

The power calculations were based on the longitudinal change from baseline in MG-ADL total score observed in REGAIN (Study ECU-MG-301 - the Phase 3 study conducted with eculizumab in refractory gMG patients). The treatment effect (difference between the eculizumab and the placebo arms in mean change (95% CI) from baseline to Week 6 for MG-ADL) was estimated to be -1.9 (-3.27, -0.55) and the estimated common SD was 3.7. Based on these parameter estimates and the assumption that Study ALXN1210-MG-306 would provide similar results, a total of N = 160 patients was required to ensure at least 90% power to reject the null hypothesis of no treatment effect for MG-ADL at the Type I error rate = 5% (2-sided) based on a t-statistic for 2 independent samples.

## Randomisation

Patients were stratified by region (North America, Europe, Asia-Pacific, and Japan) and were then randomly assigned in a 1:1 ratio to either the ravulizumab or placebo group.

## Blinding (masking)

All investigative site personnel, Sponsor staff, Sponsor designees, staff directly associated with the conduct of the study, and all patients were blinded to patient treatment assignments. The double-blind was maintained by using identical study drug kits and labels for ravulizumab and placebo. The placebo had an identical appearance to that of ravulizumab.

After the 26-Week Randomized- Controlled Period and assessments on Day 183 (Week 26), patients in the placebo group received a blinded loading dose of ravulizumab and patients in the ravulizumab group received a blinded ravulizumab dose of 900 mg.

Starting at Week 28, all patients will begin open-label ravulizumab maintenance doses q8w. For patients in the ravulizumab group, a blinded ravulizumab dose of 900 mg was chosen to ensure maintenance of complete C5 inhibition until the next scheduled maintenance dose at Week 28 (Day 197).

## Statistical methods

The primary hypothesis for this study is that ravulizumab is superior to placebo in improving MG-ADL total score at Week 26. The treatment effect based on the primary endpoint was estimated by the difference in means between the ravulizumab group and the placebo group in the change from Baseline

in MG-ADL total score at Week 26 irrespective of rescue therapy. A lower value of the corresponding estimate indicates a beneficial treatment effect.

The following secondary hypotheses were included in step-wise multiplicity adjustment (provided the null hypothesis for primary endpoint was rejected)

1. Ravulizumab is superior to placebo in improvement of QMG total score at Week 26.

2. Ravulizumab is superior to placebo in QMG 5-point response (≥ 5-point improvement from baseline in QMG total score) at Week 26.

3. Ravulizumab is superior to placebo in improvement of the MG-QOL15r total score at Week 26.

4. Ravulizumab is superior to placebo in improvement of Neuro-QOL Fatigue total score at Week 26.

5. Ravulizumab is superior to placebo in MG-ADL 3-point response (≥ 3-point improvement from baseline in MG-ADL total score) at Week 26.

The study was designed to control the overall 2-sided Type I error of $\alpha = 0.05$. The primary null hypothesis was to be tested first at $\alpha=0.05$. If statistically significant, 5 secondary hypotheses were tested for superiority using a closed-testing procedure with the following order:

1. Change from Baseline in QMG total score at Week 26

2. Proportion of patients with improvement of at least 5 points in the QMG total score from baseline at Week 26

3. Change from Baseline in MG-QOL15r at Week 26

4. Change from Baseline in Neuro-QOL Fatigue at Week 26

5. Proportion of patients with improvement of at least 3 points in the MG-ADL total score from baseline at Week 26

The testing proceeded from (#1) to (#5), and if statistical significance was not achieved (p-value >0.05), then subsequent endpoints were not considered statistically significant. Estimates and CIs were computed for all these secondary endpoints regardless of the outcome of the closed testing procedure.

Under this prespecified closed testing procedure, no adjustment of the Type I error was required.

Analysis Populations

The following analysis sets are defined in the SAP:

- Randomized Set: All patients who were randomized. Patients were analyzed according to the treatment they were randomized to receive, regardless of the treatment received.
- Full Analysis Set: All randomized patients who received at least 1 dose of study drug
- Per Protocol Set: All patients in the Full Analysis Set without any major protocol deviations during the Randomized-Controlled Period and who met all of the prespecified criteria outlined in Appendix 16.1.9 SAP Section 6.2
- Modified Full Analysis Set: A subset of patients in the Full Analysis Set which excludes patients who were impacted by COVID-19 during the Randomized-Controlled Period (details provided in Appendix 16.1.9 SAP Addendum 1.0)
- Safety Set: All patients who received at least 1 dose of study drug (ravulizumab or placebo). Patients were analyzed according to the treatment they actually received (must have received that treatment for the entire duration of the Randomized-Controlled Period).

- PK Analysis Set: All patients who received at least 1 dose of ravulizumab and who had at least 1 post-baseline PK concentration available
- Ravulizumab Treated Set: All patients who received at least 1 dose of ravulizumab either in the Randomized-Controlled Period or the Open-Label Extension Period
- Open-Label Extension Set: All patients who received at least 1 dose of ravulizumab starting from Week 26 and who have completed Week 52 study visit or who would have completed Week 52 by the data cutoff date but withdrew from the study
- Open-Label Efficacy Extension Set: All patients in the Open-Label Efficacy Extension Set who have completed Week 52 study visit or withdrew from the study prior to Week 52

The FAS will be the primary population used for the analyses of all efficacy endpoints for the Randomized-Controlled Period. Sensitivity analyses of the primary and secondary efficacy endpoints will also be conducted using the PPS. The Randomized-Controlled Period Baseline is defined as the last available assessment value prior to first study drug infusion. In general, the baseline assessment will be the Day 1 assessment. For QMG and MGC, in the event that cholinesterase inhibitor was not withheld for at least 10 hours prior to administration of the QMG and MGC tests, the Screening Visit assessment will be used as Baseline. If cholinesterase inhibitor was not withheld for at least 10 hours for these visits, the Day 1 assessment will be used as Baseline.

Efficacy analyses of MG-ADL and QMG total scores will be performed on the OLEES. The OLE Baseline is defined as the last available assessment prior to first study drug administered in the OLE Period. In general, the OLE Baseline assessment will be the Day 183 assessment. In the event that cholinesterase inhibitor was not withheld for at least 10 hours prior to administration of the QMG test, the prior visit assessment will be used as baseline.

Primary Analysis

The primary endpoint is change from Baseline in MG-ADL total score at Week 26 of the Randomized-Controlled Period.

Change from Baseline in MG-ADL total score at Week 26 was analyzed using a mixed-effect model for repeated measures (MMRM; [Mallinckrodt 2001, 2004]). The model will include the MG-ADL change from Baseline score at each prespecified time point (Weeks 1, 2, 4, 10, 12, 18, and 26) as the response variable, fixed categorical effects of treatment, study visit and treatment-by-study visit interaction, the randomization stratification variable region; as well as fixed covariate of baseline MG-ADL total score. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each patient. If this analysis fails to converge, the following structures will be tested and the final covariance structure will be determined by Akaike's information criterion: first order autoregressive, compound symmetry, and Toeplitz method. A difference in treatment effect between the ravulizumab and placebo treatment groups along with a 2-sided 95% confidence interval (CI) and p-value will be calculated. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. Missing data will not be imputed for the primary analysis. Similar summaries will be presented for the other Randomized-Controlled Period study visits. Absolute levels and the change in MG-ADL total score will be summarized by treatment group and visit.

Subgroup Analyses

The following subgroups by treatment group were considered: Region, gender, race, age at first study drug infusion (18 to 65 years and > 65 years), IST use at baseline (corticosteroid, corticosteroid + IST, none), years from diagnosis to informed consent (≤ median, >median), MGFA (II, III, and IV), and baseline body weight categories (≥ 40 to < 60 kg, ≥ 60 to < 100 kg, and ≥ 100 kg). If the number of

patients for a given subgroup category was less than 10, then the category maybe collapsed with another category.

Amendments of the analysis plan Prior to Unblinding or Database Lock

Additional analyses were implemented through Addendum 1.0 (dated 03 Dec 2020) and Addendum 2.0 Version 1.0 (dated 10 Jun 2021) to the final SAP.

The SAP Addendum 1.0 included changes required to address the impact of COVID-19 on the planned analyses as described in the Final SAP Version 1.0. The study objectives for this study did not change. Additionally, the originally planned statistical methodology as specified in SAP Version 1.0 has not changed.

The SAP Addendum 2.0 included additional summaries of MG therapies for the Safety Set, additional MG therapy categories for subgroups for primary and secondary endpoint analyses of the Full Analysis Set, additional covariance structures in the mixed-effect model for repeated measures (MMRM) for the secondary endpoints of at least 3-point improvement in MG-ADL and at least 5-point improvement in QMG from baseline to Week 26, and a summary of treatment-emergent AEs during the Randomized-Controlled Period utilizing standardised Medical Dictionary for Regulatory Activities (MedDRA) query (narrow) (SMQ[N]) of hypersensitivity for the Safety Set (to replace the infusion-related reaction summary).

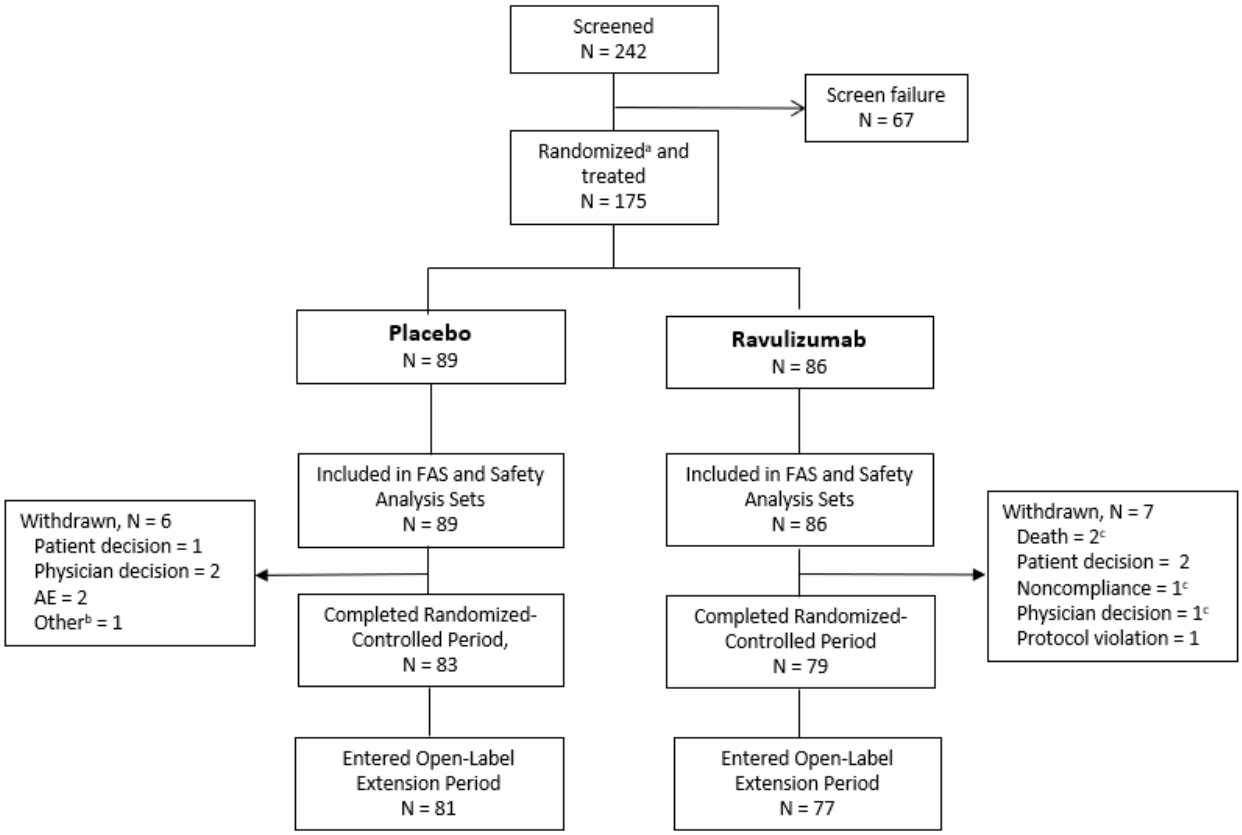
## *Results*

## Participant flow

Of the 242 screened patients, 67 patients were screen failures. The most common (≥ 5%) reasons for screen failure were not having a positive serologic test for anti-AChR antibodies at screening (n = 25) and not having an MG-ADL profile ≥ 6 (n = 16). Twenty-two patients failed initial screening but met all entry criteria upon second screening and were subsequently enrolled in the study.

In total, 175 patients were randomized and treated (placebo: N = 89; ravulizumab: N = 86) (Figure 9). Thirteen patients withdrew from the study prior to completing the Randomized-Controlled Period: 3 due to patient decision; 3 due to physician decision, 2 due to AEs ; 2 deaths (cerebral hemorrhage and COVID-19 pneumonia; 1 due to noncompliance with study drug; 1 due to protocol violation, and 1 due to other/Sponsor decision.

As of the clinical data cutoff date, 75 of the 79 patients in the Open-Label Extension Set (ie, patients who had received at least 1 dose of ravulizumab starting from Week 26 and who had reached Week 52 or would have completed the Week 52 Visit by the data cutoff dates but had withdrawn from the study prior to Week 52) had completed the Week 52 Visit (Table 20). Four of the 79 patients in the Open-Label Extension Set had withdrawn from the study during the Open-Label Extension Period (2 due to patient decision and 2 deaths due to COVID-19).




a Two additional patients were randomized in error: 1 patient was randomized but could not be dosed due to a water leak in the laminar hood while preparing study drug; patient was ultimately screen failed. Additionally, 1 patient was randomized and screen failed due to pyridostigmine not being withheld 10 hours prior to Screening assessments; this patient was subsequently re-screened and re-randomized (patient was counted in the "Randomized and treated" row).
b Other reason = Sponsor's request, measuring complement-related protein that could have led to potential unblinding (ie, the assessment would be biased)
c Three patients in the ravulizumab group withdrew from the study for reasons related to COVID-19 during the Randomized-Controlled Period (1 death, 1 due to noncompliance, 1 due to physician decision).
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; FAS = Full Analysis Set

**Table 20: Patient Disposition During the Open-label Extension Period (Open-label Extension Set)**

| | Placebo to Ravulizumab (N=41) | Ravulizumab to Ravulizumab (N=38) | Total (N=79) |
|---|---|---|---|
| | Overall | Overall | Overall |
| Entered into Open-label Extension Period, n (%) | 41 (100) | 38 (100) | 79 (100) |
| Treated, n (%) | 41 (100) | 38 (100) | 79 (100) |
| Ongoing in Open-label Extension Period at data cutoff, n (%) | 40 (97.6) | 35 (92.1) | 75 (94.9) |
| Discontinued Open-label Extension Period, n (%) | 1 (2.4) | 3 (7.9) | 4 (5.1) |
| Death | 1 (2.4) | 1 (2.6) | 2 (2.5) |
| Withdrawal by patient | 0 | 2 (5.3) | 2 (2.5) |

Note: The Open-Label Extension Set consisted of all patients who received at least 1 dose of ravulizumab in the Open-Label Extension Period. Only patients reaching Week 52 or expected to reach Week 52 by the time of data cutoff were included.

## Recruitment

Patients were enrolled in 85 sites across 13 countries (Canada, Czech Republic, Denmark, France, Germany, Israel, Italy, Japan, The Netherlands, South Korea, Spain, Switzerland, and the US).

Date first patient enrolled: 26 Mar 2019

Data cutoff date: 11 May 2021

## Conduct of the study

Since the original protocol (dated 16 Nov 2018), 2 global protocol amendments and other country-specific amendments have been made as of the data cut-off date of 11 May 2021.

**Table 21: Summary of Protocol Changes**

| Amendment Number (Country) Date | Summary of Key Changes in the Amendment |
|---|---|
| Amendment 1 (Global)<br>11 Dec 2018 | The purpose of this amendment was to change duration of safety follow-up after last dose; add additional details on assessments, align pregnancy and clinical laboratory testing frequency with infusions; change supplemental dosing recommendations and sample collection when rescue therapy is provided; and update adverse event and pregnancy/contraception language. |
| Amendment 1.1 (Germany)<br>27 Jun 2019 | The purpose of this amendment was to exclude enrollment of patients with active systemic infections, as requested by Germany's competent national agency Paul-Ehrlich-Institut. |
| Amendment 1.2 (France)<br>14 Oct 2019 | The purpose of this amendment was to exclude enrollment of patients with active systemic infections, in answer to request by the French competent national agency, Agence Nationale de Sécurité du Médicament et des Produits de Santé. |
| Amendment 1.3 (United Kingdom)<br>11 Nov 2019 | The purpose of this amendment was to comply with Good Clinical Practice Inspectors Working Group and Clinical Trial Facilitation Group guidelines which specify that the responsibility to break the treatment code in emergency situations resides solely with the Investigator. |
| Amendment 2 (Global)<br>25 Oct 2019 | The purpose of this amendment was to revise secondary and exploratory endpoints, to decrease burden to patients by reduction in assessment and visit frequency, to provide additional guidance for supplemental dosing, and to clarify minor operational aspects of the protocol. |
| Amendment 2.1 (United Kingdom)<br>13 Dec 2019 | The purpose of this amendment was to revise secondary and exploratory endpoints, to decrease burden to patients by reduction in assessment and visit frequency, to provide additional guidance for supplemental dosing, and to clarify minor operational aspects of the protocol. |
| Amendment 2.2 (France)<br>02 Jun 2020 | The purpose of this amendment was to provide the instruction of visits at home or alternative healthcare facilities during the COVID-19 pandemic. |
| Amendment 2.3 (Spain, Germany, Japan)<br>02 Feb 2021 | The purpose of this amendment was to transition all patients in specified countries from the 10 mg/mL formulation to the 100 mg/mL formulation of ravulizumab during the Open-Label Extension Period. |

| | |
|---|---|
| Amendment 2.4 (France)<br>02 Feb 2021 | The main purpose of this amendment is to transition all patients in specified countries from the 10 mg/mL formulation to the 100 mg/mL formulation of ravulizumab during the Open-Label Extension Period. |

Abbreviation: COVID-19 = coronavirus disease 2019

Important deviations were reported for 41 (23.4%) patients during the Randomized-Controlled Period (Table 22). Additional details on each type of deviation are provided below.

Following the assessment of all important protocol deviations, Alexion concluded that none were considered to have impacted the safety of the patients or the reliability of the study data.

**Table 22: Patients with Important Protocol Deviations During the Randomized-Controlled Period (Full Analysis Set)**

| | Placebo (N = 89) | | Ravulizumab (N = 86) | | Total (N = 175) | |
|---|---|---|---|---|---|---|
| | Overall n (%) | COVID-19 related n (%) | Overall n (%) | COVID-19 related n (%) | Overall n (%) | COVID-19 related n (%) |
| At least 1 deviation | 21 (23.6) | 7 (7.9) | 20 (23.3) | 3 (3.5) | 41 (23.4) | 10 (5.7) |
| Eligibility and entry criteria | 0 | 0 | 2 (2.3) | 0 | 2 (1.1) | 0 |
| Investigational product | 8 (9.0) | 5 (5.6) | 4 (4.7) | 3 (3.5) | 12 (6.9) | 8 (4.6) |
| Concomitant medication | 1 (1.1) | 0 | 2 (2.3) | 0 | 3 (1.7) | 0 |
| Informed consent | 0 | 0 | 3 (3.5) | 0 | 3 (1.7) | 0 |
| Laboratory assessment | 0 | 0 | 0 | 0 | 0 | 0 |
| Visit schedule | 0 | 0 | 0 | 0 | 0 | 0 |
| Study procedures/tests | 8 (9.0) | 3 (3.4) | 7 (8.1) | 1 (1.2) | 15 (8.6) | 4 (2.3) |
| Randomization | 1 (1.1) | 0 | 0 | 0 | 1 (0.6) | 0 |
| Safety reporting | 6 (6.7) | 0 | 5 (5.8) | 0 | 11 (6.3) | 0 |
| Source document | 1 (1.1) | 1 (1.1) | 0 | 0 | 1 (0.6) | 1 (0.6) |
| Other | 0 | 0 | 0 | 0 | 0 | 0 |

Note: Percentages were based on the number of patients in the respective treatment group and may add to more than 100% since a patient may have more than 1 important protocol deviation. Protocol deviations due to COVID-19 are also presented in the overall column.
Abbreviation: COVID-19 = coronavirus disease 2019

Since this study was conducted during the COVID 19 pandemic, it was anticipated that some patients would not be able to travel to the study site on the protocol-specified visit days and would potentially receive study drug outside of the dosing window. Therefore, the calculation for treatment compliance was modified from being based on the "number of scheduled doses given/number of expected scheduled doses" to reflect the percentage of time during the Randomized-Controlled Period that patients were considered to have complete terminal complement inhibition (ie, 100% – sum [percentage of time patients were noncompliant with scheduled doses]).

## Baseline data

**Table 23: Demographics and Baseline Characteristics (Full Analysis Set)**

| Variable | Placebo (N = 89) | Ravulizumab (N = 86) | Total (N = 175) |
|---|---|---|---|
| Sex, n (%) | | | |
| Male | 44 (49.4) | 42 (48.8) | 86 (49.1) |
| Female | 45 (50.6) | 44 (51.2) | 89 (50.9) |
| Ethnicity, n (%) | | | |
| Not Hispanic or Latino | 78 (87.6) | 79 (91.9) | 157 (89.7) |
| Not reported | 5 (5.6) | 3 (3.5) | 8 (4.6) |
| Hispanic or Latino | 5 (5.6) | 2 (2.3) | 7 (4.0) |
| Unknown | 1 (1.1) | 2 (2.3) | 3 (1.7) |
| Race, n (%) | | | |
| White | 61 (68.5) | 67 (77.9) | 128 (73.1) |
| Asian | 16 (18.0) | 15 (17.4) | 31 (17.7) |
| Not reported | 5 (5.6) | 2 (2.3) | 7 (4.0) |
| Black or African American | 4 (4.5) | 2 (2.3) | 6 (3.4) |
| American Indian or Alaska Native | 1 (1.1) | 0 | 1 (0.6) |
| Other | 1 (1.1) | 0 | 1 (0.6) |
| Unknown | 1 (1.1) | 0 | 1 (0.6) |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| Age at first infusion (years) | | | |
| Mean (SD) | 53.3 (16.05) | 58.0 (13.82) | 55.6 (15.14) |
| Median | 55.0 | 61.5 | 58.0 |
| Min, max | 20, 82 | 19, 79 | 19, 82 |
| Age at first infusion (years) category, n (%) | | | |
| 18 to 65 years | 65 (73.0) | 56 (65.1) | 121 (69.1) |
| > 65 years | 24 (27.0) | 30 (34.9) | 54 (30.9) |
| Baseline weight (kg) | | | |
| Mean (SD) | 90.9 (29.45) | 91.6 (23.37) | 91.2 (26.57) |
| Median | 89.0 | 91.7 | 90.0 |
| Min, max | 44.1, 185.0 | 40.0, 165.8 | 40.0, 185.0 |
| Baseline weight (kg) category, n (%) | | | |
| ≥ 40 to < 60 kg | 11 (12.4) | 7 (8.1) | 18 (10.3) |
| ≥ 60 to < 100 kg | 47 (52.8) | 47 (54.7) | 94 (53.7) |
| ≥ 100 kg | 31 (34.8) | 32 (37.2) | 63 (36.0) |
| Region randomization stratification, n (%) | | | |
| North America | 40 (44.9) | 40 (46.5) | 80 (45.7) |
| Europe | 33 (37.1) | 31 (36.0) | 64 (36.6) |
| Asia-Pacific | 9 (10.1) | 9 (10.5) | 18 (10.3) |
| Japan | 7 (7.9) | 6 (7.0) | 13 (7.4) |

Note: Percentages were based on the total number of patients in each group. Baseline was defined as the last available assessment value prior to first study drug infusion.
Abbreviations: max = maximum; min = minimum

Disease characteristics at baseline are summarized in Table 24.

**Table 24: Baseline Disease Characteristics (Full Analysis Set)**

| Variable<br>Category | Placebo<br>(N = 89) | Ravulizumab<br>(N = 86) | Total<br>(N = 175) |
|---|---|---|---|
| Age (years) at MG diagnosis | | | |
| Mean (SD) | 43.7 (19.04) | 48.6 (18.54) | 46.1 (18.91) |
| Median | 44.8 | 50.4 | 47.9 |
| Min, max | 12, 81 | 12, 77 | 12, 81 |
| Years from MG diagnosis to informed consent | | | |
| Mean (SD) | 10.0 (8.90) | 9.8 (9.68) | 9.9 (9.27) |
| Median | 7.6 | 5.7 | 6.5 |
| Min, max | 0.5, 36.1 | 0.5, 39.5 | 0.5, 39.5 |
| Type of first MG clinical presentation, n (%) | | | |
| Ocular MG | 29 (32.6) | 21 (24.4) | 50 (28.6) |
| Generalized MG (gMG) | 60 (67.4) | 65 (75.6) | 125 (71.4) |
| Time to gMG, if first presentation was ocular MG (months) | | | |
| n | 28 | 20 | 48 |
| Mean (SD) | 24.1 (54.01) | 15.2 (31.20) | 20.4 (45.71) |
| Median | 6.0 | 3.0 | 4.0 |
| Min, max | 1.0, 288.0 | 1.0, 120.0 | 1.0, 288.0 |
| Maximum MGFA clinical classification prior to Screening, n (%) | | | |
| Class IIa | 10 (11.2) | 12 (14.0) | 22 (12.6) |
| Class IIb | 8 (9.0) | 12 (14.0) | 20 (11.4) |
| Class IIIa | 23 (25.8) | 12 (14.0) | 35 (20.0) |
| Class IIIb | 18 (20.2) | 24 (27.9) | 42 (24.0) |
| Class IVa | 9 (10.1) | 5 (5.8) | 14 (8.0) |
| Class IVb | 12 (13.5) | 12 (14.0) | 24 (13.7) |
| Class V | 9 (10.1) | 8 (9.3) | 17 (9.7) |
| Baseline MGFA clinical classification, n (%) | | | |
| Class IIa | 24 (27.0) | 22 (25.6) | 46 (26.3) |
| Class IIb | 15 (16.9) | 17 (19.8) | 32 (18.3) |
| Class IIIa | 34 (38.2) | 22 (25.6) | 56 (32.0) |
| Class IIIb | 11 (12.4) | 19 (22.1) | 30 (17.1) |
| Class IVa | 4 (4.5) | 2 (2.3) | 6 (3.4) |
| Class IVb | 1 (1.1) | 4 (4.7) | 5 (2.9) |
| Baseline MG-ADL total score | | | |
| Mean (SD) | 8.9 (2.30) | 9.1 (2.62) | 9.0 (2.46) |

**Table 24: Baseline Disease Characteristics (Full Analysis Set) (cont.)**

| Variable<br>Category | Placebo<br>(N = 89) | Ravulizumab<br>(N = 86) | Total<br>(N = 175) |
|---|---|---|---|
| Median<br>Min, max | 9.0<br>6.0, 15.0 | 9.0<br>6.0, 24.0 | 9.0<br>6.0, 24.0 |
| Baseline QMG total score<br>Mean (SD)<br>Median<br>Min, max | <br>14.5 (5.26)<br>14.0<br>2.0, 27.0 | <br>14.8 (5.21)<br>15.0<br>6.0, 39.0 | <br>14.7 (5.22)<br>15.0<br>2.0, 39.0 |
| Ventilator support any time prior to Screening, n (%)<br>Yes<br>No | <br>13 (14.6)<br>76 (85.4) | <br>17 (19.8)<br>69 (80.2) | <br>30 (17.1)<br>145 (82.9) |
| MG exacerbation including crisis events prior to Screening, n (%)<br>Yes<br>No | <br>57 (64.0)<br>32 (36.0) | <br>58 (67.4)<br>28 (32.6) | <br>115 (65.7)<br>60 (34.3) |
| Total number of patients with MG exacerbations prior to Screening, n (%) | 53 (59.6) | 52 (60.5) | 105 (60.0) |
| Total number of patients taking MG medications at time of MG exacerbations, n (%) | 51 (57.3) | 47 (54.7) | 98 (56.0) |
| Total number of MG exacerbations prior to Screening, n | 169 | 100 | 269 |
| Total patient-years prior to Screening[a] | 887.0 | 846.8 | 1733.8 |
| Rate of MG exacerbations / 100 PY | 19.1 | 11.8 | 15.5 |
| Total number of patients with MG crisis[b] events prior to Screening, n (%) | 17 (19.1) | 21 (24.4) | 38 (21.7) |
| Total number of patients taking MG medications at time of MG crisis[b] events, n (%) | 17 (19.1) | 19 (22.1) | 36 (20.6) |
| Total number of MG crisis[b] events prior to Screening, n | 33 | 35 | 68 |
| Rate of MG crisis[b] events / 100 PY | 3.7 | 4.1 | 3.9 |

Prior Therapy

Overall, usage of *non-MG medications* prior to the start of the study was similar between the placebo and ravulizumab groups. The most commonly used (in ≥ 25% of total patients) non-MG medications were drugs for peptic ulcer and gastro-oesophageal reflux disease (49.7%); lipid-modifying agents, plain (34.9%); and vitamin A and D, including combinations of the two (32.0%).

All patients used *MG therapy* (including symptomatic therapies) prior to the start of the study and usage was similar between the placebo and ravulizumab groups. Overall, the most common (in ≥ 25% of total patients) MG medications used prior to study treatment were pyridostigmine bromide (77.7%), prednisone (51.4%), mycophenolate mofetil (32.6%), azathioprine (31.4%), and immunoglobulins not otherwise specified (28.6%). The majority (50.9%) of patients used only 2 ISTs with the most common (20%) combination being corticosteroids and mycophenolate mofetil. Within 2 years prior to Screening, 19.4% of patients used any PE/PP and 43.4% of patients used IVIg.

Concomitant Therapy

Overall, 97.7% of patients (100% in the ravulizumab and 95.5% in placebo group) took at least 1 *non-MG concomitant medication* during the Randomized-Controlled Period. Of note, patients in the ravulizumab group used lipid modifying agents (ravulizumab: 44.2%; placebo: 27.0%), blood glucose lowering drugs, excluding insulin (ravulizumab: 29.1%; placebo: 19.1%), and selective calcium channel

blockers with mainly vascular effects (ravulizumab: 22.1%; placebo: 12.4%) more than those patients in the placebo group.

The most commonly reported (in ≥ 25% of patients) groupings of concomitant non-MG medications other than meningococcal vaccine were drugs for peptic ulcer and gastro-esophageal reflux disease (52.6%); other analgesics and antipyretics (41.1%); lipid-modifying agents, plain (35.4%); vitamin A and D, including combinations of the two (35.4%); antithrombotic agents (26.9%); anti-inflammatory and antirheumatic products, non-steroids (25.7%); and calcium (25.1%).

Regarding *MG medications*, a majority of patients (69.1%) were taking corticosteroids at the time of their first dose of study drug in the Randomized-Controlled Period (placebo: 73.0%; ravulizumab 65.1%). Almost half (47.4%) of patients were using only 2 ISTs (placebo: 52.8%; ravulizumab 41.9%); the most common (18.3%) combination was corticosteroids and mycophenolate mofetil (placebo: 22.5%; ravulizumab 14.0%).

A majority (70.3%) of patients continued to take corticosteroids during the Randomized-Controlled Period (placebo: 74.2%; ravulizumab 66.3%). Change (introduction, discontinuation, or increased or decreased dosage) of ISTs occurred in 24% of patients overall (placebo: 21%; ravulizumab 27%) during the Randomized-Controlled Period. The most common change was use of new immunoglobulins due to MG symptoms worsening (10.0%). Most of the changes in ISTs were either allowable or not clinically significant.

Overall, MG medications (other than IVIg) used by ≥ 25% of patients during the Randomized-Controlled Period were pyridostigmine bromide (65.7%), prednisone (45.1%), and mycophenolate mofetil (26.9%).

During the Randomized-Controlled Period, 10.3% of patients used IVIg (placebo: 14.6%; ravulizumab: 5.8%) and 1.7% of patients used any PE/PP (placebo: 1.1%; ravulizumab: 2.3%).

All patients used concomitant MG medications during the Open-Label Extension Period. Overall, concomitant MG medications (other than IVIg) used in ≥ 25% of patients during the Open-Label Extension Period were pyridostigmine bromide (64.6%), prednisone (54.4%), and mycophenolate mofetil (34.2%).

The most commonly used IST during the Open-Label Extension Period was corticosteroids (72.2%). A total of 39.2% of patients used only 2 ISTs during the Open-Label Extension Period, with the most common (21.5%) combination being corticosteroids and mycophenolate mofetil.

During the Open-Label Extension Period, 6.3% of patients used IVIg and 3.8% of patients used any PE/PP.

In the Open-Label Extension Period of the study, physicians had the option to adjust IST therapies. Approximately half (50.6%) of patients had a change in concomitant MG medication during the Open-Label Extension Period. The most common change was a decrease in corticosteroids for systemic use, plain due to MG symptoms improved (26.6%)

Compliance

During the Randomized-Controlled Period, treatment compliance was 94.4% in the placebo group and 96.5% in the ravulizumab group. Including the Open-Label Extension Period for the subset of patients who reached (or would have reached) 52 weeks of exposure as of the data cutoff date, the mean (SD) ravulizumab exposure presented in this safety summary is 234.3 (86.65) days in 127 patients: 258.2 (96.48) days in 86 patients randomized to ravulizumab and 184 (6.78) days in 41 patients randomized to placebo who switched to ravulizumab during the Open-Label Extension Period. The majority (92.9%) of patients had 100% treatment compliance during the Ravulizumab Treatment Period (ie, since the first dose of ravulizumab).

## Numbers analysed

**Table 25: Analysis Sets (All Randomized Patients)**

| | Placebo n (%) | Ravulizumab n (%) | Total n (%) |
|---|---|---|---|
| Randomized[a] | 89 | 86 | 175 |
| Safety Analysis Set | 89 (100) | 86 (100) | 175 (100) |
| Full Analysis Set | 89 (100) | 86 (100) | 175 (100) |
| Per Protocol Set | 79 (88.8) | 76 (88.4) | 155 (88.6) |
| Excluded | 10 (11.2) | 10 (11.6) | 20 (11.4) |
| Eligibility criteria not met | 0 | 2 (2.3) | 2 (1.1) |
| Wrong study drug taken | 0 | 0 | 0 |
| Cholinesterase inhibitor taken within 10 hours prior to QMG and MGC at Baseline or Week 26 | 3 (3.4) | 3 (3.5) | 6 (3.4) |
| Missed at least 1 scheduled dose | 5 (5.6) | 3 (3.5) | 8 (4.6) |
| Did not receive at least 1 supplemental dose at the conclusion of rescue therapy | 0 | 0 | 0 |
| Changes in background MG medications | 1 (1.1) | 1 (1.2) | 2 (1.1) |
| Emergency unblinding | 0 | 0 | 0 |
| Received rescue medications on Day 1 | 0 | 0 | 0 |
| Other major protocol deviations[b] | 1 (1.1) | 1 (1.2) | 2 (1.1) |
| Modified Full Analysis Set | 85 (95.5) | 80 (93.0) | 165 (94.3) |
| Excluded[c] | 4 (4.5) | 6 (7.0) | 10 (5.7) |
| Had a COVID-19 related AE during Randomized-Controlled Period | 4 (4.5) | 5 (5.8) | 9 (5.1) |
| Missed 2 consecutive scheduled doses during Randomized-Controlled Period due to COVID-19 | 0 | 1 (1.2) | 1 (0.6) |
| Terminated early during Randomized-Controlled Period due to COVID-19 | 0 | 3 (3.5) | 3 (1.7) |
| Treated for COVID-19 during Randomized-Controlled Period with MG medications | 0 | 3 (3.5) | 3 (1.7) |
| PK Analysis Set | 89 (100) | 86 (100) | 175 (100) |
| Open-Label Extension Set[d] | 41 (46.1) | 38 (44.2) | 79 (45.1) |
| Excluded | 0 | 5 (5.8) | 5 (2.9) |
| No open-label treatment received | 0 | 5 (5.8) | 5 (2.9) |
| Ravulizumab Treated Set[e] | 41 (46.1) | 86 (100) | 127 (72.6) |

[a] Two additional patients were randomized in error: 1 patient was randomized but could not be dosed due to a water leak in the laminar hood while preparing study drug; patient was ultimately screen failed. Additionally, 1 patient was randomized and screen failed due to pyridostigmine not being withheld 10 hours prior to Screening assessments; this patient was subsequently re-screened and re-randomized (patient was counted in the randomized and treated row)

[b] One patient (ravulizumab group) did not complete the spirometry assessments during the Randomized-Controlled Period and 1 patient (placebo group) had C3, C4, and CH50 tests performed during the study which could have led to unblinding (Listing 16.2.2.3.1.2).

[c] Patients may have been counted in more than 1 category for the reason for exclusion.

[d] The Open-Label Extension Set consisted of all patients who received at least 1 dose of ravulizumab in the Open-Label Extension Period. Per scope, only patients reaching Week 52 or expected to reach Week 52 by the time of data cutoff were included.

[e] The Ravulizumab Treated Set consisted of all patients who received at least 1 dose of ravulizumab either in the Randomized-Controlled Period or the Open-Label Extension Period. Per scope, only data during Randomized-Controlled Period were included for patients not expected to have reached Week 52 at data cutoff. This applied to both ravulizumab and placebo patients.

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; MGC = Myasthenia Gravis Composite; MG = myasthenia gravis; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis

## Outcomes and estimation

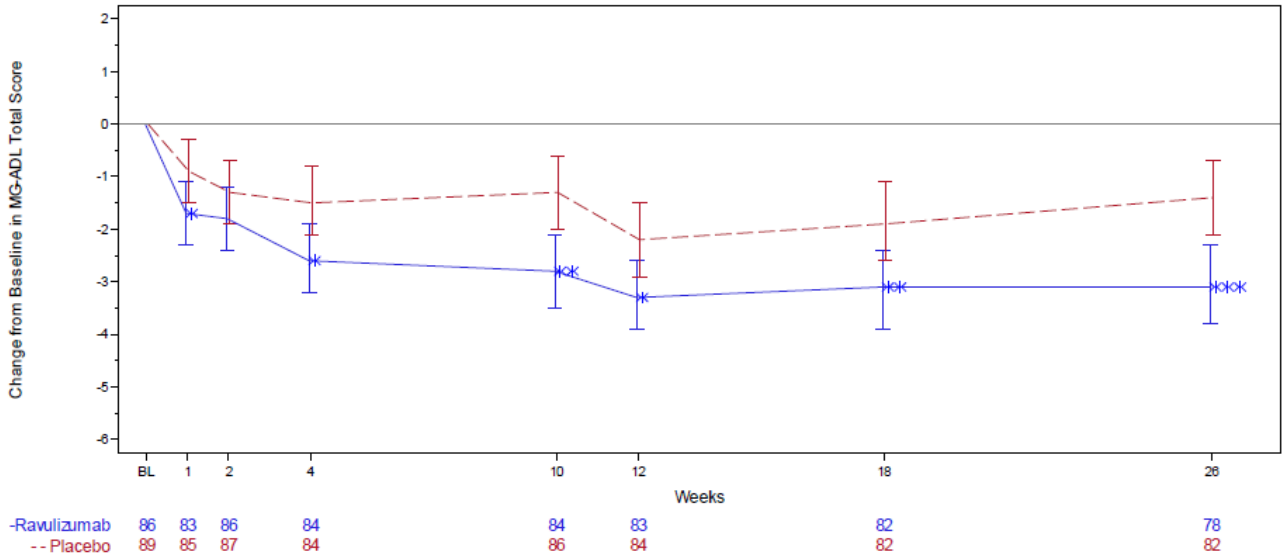
### *Primary Efficacy Endpoint*

MG-ADL Total Score

The least-squares (LS) mean (SEM) reduction from Baseline to Week 26 in MG-ADL total score was significantly greater in the ravulizumab group (-3.1 [0.38]) compared to the placebo group (-1.4 [0.37]) during the Randomized-Controlled Period (mean treatment difference: -1.6 [0.49]; 95% confidence interval [CI]: -2.6, -0.7; p = 0.0009).

In the ravulizumab group, improvement in MG-ADL total score was observed as early as Week 1 with improvement sustained through Week 26 (Figure 10).

**Figure 10: Change from Baseline in MG-ADL Total Score During the Randomized-Controlled Period (Full Analysis Set)**




Note: Baseline was defined as the last available assessment value prior to first study drug infusion. Estimates were based on MMRM that included treatment group, stratification factor region, and MG-ADL total score at baseline, study visit, and study visit by treatment group interaction. P-values were for the comparison of treatment groups in change from baseline. An unstructured covariance structure was used.
* = p < 0.05, ** = p < 0.01, and *** = p < 0.001 represent 2-sided nominal p-values.

The change from Baseline in MG-ADL total score to Week 26 was consistent with the Full Analysis Set for the Per Protocol Set and Modified Full Analysis Set.

*Sensitivity Analyses*

The actual change from Baseline in the MG-ADL total score to Week 26 using pre-specified sensitivity analysis is summarized for the Full Analysis Set. The results of the sensitivity analysis supported the results of the primary analysis (Table 26).

**Table 26: Sensitivity Analyses for MG-ADL from Baseline to Week 26**

| Analysis Population | LS Mean Treatment Difference (SEM) | 95% CI | P-values |
|---|---|---|---|
| Full Analysis Set | -1.6 (0.49) | -2.6, -0.7 | 0.0009 |
| MMRM placebo-based | -1.6 (0.49) | -2.6, -0.7 | 0.0010 |
| MMRM tipping point (occurs at shift of 6.5 points p-value = 0.0571) | -1.07 (0.56) | -2.18, 0.03 | 0.0571 |
| MMRM excluding the randomization stratification region from the model | -1.7 (0.49) | -2.6, -0.7 | 0.0008 |
| MMRM including rescue therapy received (Yes/No) during the Randomized-Controlled Period in the model | -1.6 (0.47) | -2.5, -0.6 | 0.0011 |
| Per Protocol Set | -1.7 (0.49) | -2.7, -0.7 | 0.0006 |
| Modified Full Analysis Set | -1.8 (0.49) | -2.8, -0.9 | 0.0002 |

Abbreviations: CI = confidence interval; LS = least square; MG-ADL = Myasthenia Gravis-Activities of Daily Living; MMRM = mixed-effect model for repeated measures; SEM = standard error of the mean

### *Secondary Efficacy Endpoints*

A statistically significant improvement was observed in the ravulizumab group compared to the placebo group for the first 2 of the 5 secondary endpoints (ie, QMG and QMG responder) according to a prespecified hierarchical testing order (Table 27). Since the treatment difference did not reach statistical significance for the change from baseline in MG QoL15r total score assessment (p = 0.0636), nominal p values are presented for change from Baseline in Neuro QoL Fatigue score and improvement of at least 3 points in MG ADL total score at Week 26. Results for all secondary endpoints consistently favoured ravulizumab compared to placebo.

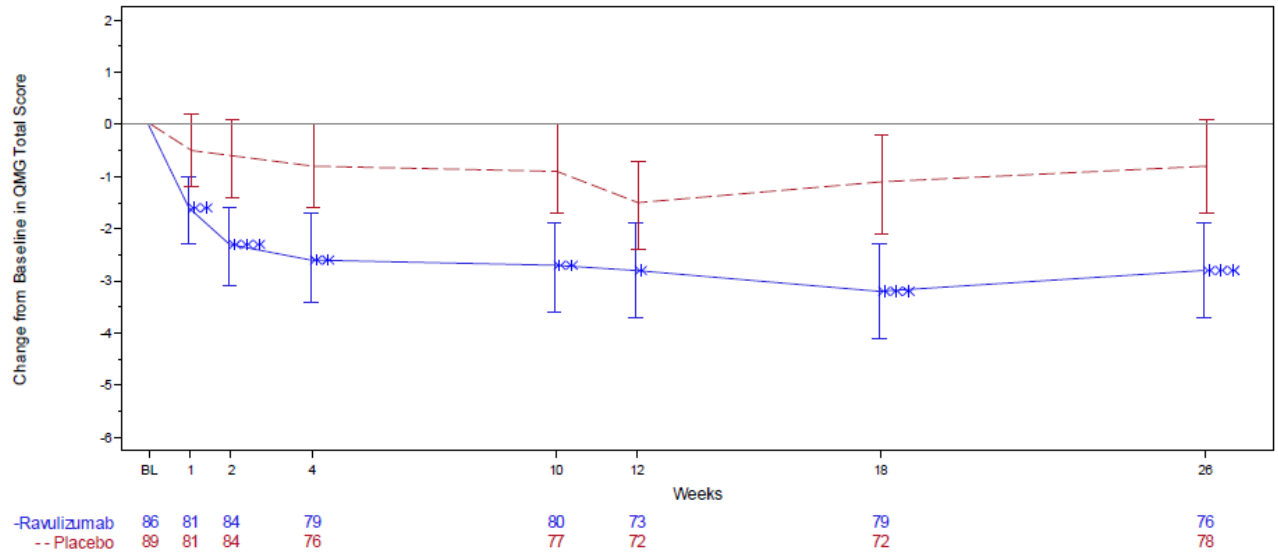
**Table 27: ALXN1210-MG-306 Efficacy Results**

| | **Ravulizumab (n =86) LS Mean (SEM)*** | **Placebo (n = 89) LS Mean (SEM)*** | **Statistic for Comparison** | **Treatment Effect (95% CI)** | **p-value (MMRM)** |
|---|---|---|---|---|---|
| **Secondary Efficacy Endpoints at Week 26** | | | | | |
| QMG Total Score | -2.8 (0.46) | -0.8 (0.45) | Difference in Change from Baseline | -2.0 (-3.2 , -0.8) | 0.0009 |
| QMG ≥5-point improvement* | 30.0% | 11.3% | Odds ratio | 3.350 (1.443 , 7.777) | 0.0052 |
| MG-QOL15r | -3.3 (0.71) | -1.6 (0.70) | Difference in Change from Baseline | -1.7 (-3.4 , 0.1) | 0.0636 |
| Neuro-QOL-fatigue | -7.0 (1.92) | -4.8 (1.87) | Difference in Change from Baseline | -2.2 (-6.9 , 2.6) | 0.3734** |
| 5. MG-ADL ≥3-point improvement* | 56.7% | 34.1% | Odds ratio | 2.526 (1.330 , 4.799) | 0.0049** |

*Adjusted percentages within each treatment are displayed.
** Nominal p-values
Note: Secondary efficacy endpoints were tested in a hierarchical approach (numbers included for testing order). Hierarchical testing proceeded from 1 to 5, and if statistical significance was not achieved (p-value > 0.05), then subsequent endpoints were not considered statistically significant and all displayed p-values from analyses of lower hierarchy were to be considered nominal.
Abbreviations: CI= Confidence Interval, LS = Least Squares; MG-ADL=MG Activities of Daily Living total score,
MG-QoL15r= Revised 15-Component Myasthenia Gravis Quality of Life, MMRM = mixed-effect model for repeated measures;
Neuro-QOL-fatigue = Neurological Quality of Life Fatigue, QMG = Quantitative MG total score,
SEM = Standard Error of Mean.

Change from Baseline in QMG Total Score

**Figure 11: Change from Baseline in QMG Total Score During the Randomized-Controlled Period (Full Analysis Set)**




Note: Baseline was defined as the last available assessment value prior to first study drug infusion. In the event that cholinesterase inhibitor was not withheld for at least 10 hours prior to administration of the QMG assessment, the Screening visit assessment was used as Baseline. Estimates were based on MMRM that included treatment group, stratification factor region and QMG total score at baseline, study visit, and study visit by treatment group interaction. P-values were for the comparison of treatment groups in change from baseline. An unstructured covariance structure was used.

* = $p<0.05$, ** = $p<0.01$, and *** = $p<0.001$ represent 2-sided nominal p-values.

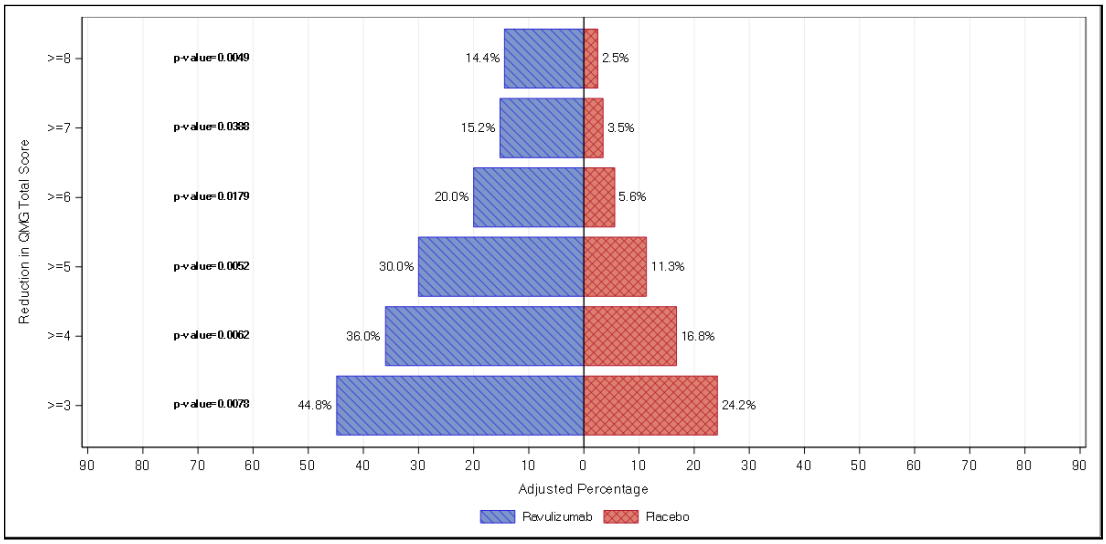
Abbreviations: BL = Baseline; MMRM = mixed-effect model for repeated measures; QMG = Quantitative Myasthenia Gravis

The change from Baseline in the QMG total score to Week 26 was consistent with the Full Analysis Set for the Per Protocol Set and Modified Full Analysis.

QMG 5-point Response

There was a significantly larger proportion of clinical responders in the ravulizumab group than in the placebo group based on a ≥ 5-point reduction in the QMG total score from Baseline to Week 26 (odds ratio [OR]: 3.350; 95% CI: 1.443, 7.777; p = 0.0052) during the Randomized-Controlled Period.

**Figure 12: Proportion of Patients with Various Point Reductions in QMG Total Score at Week 26 (Full Analysis Set)**

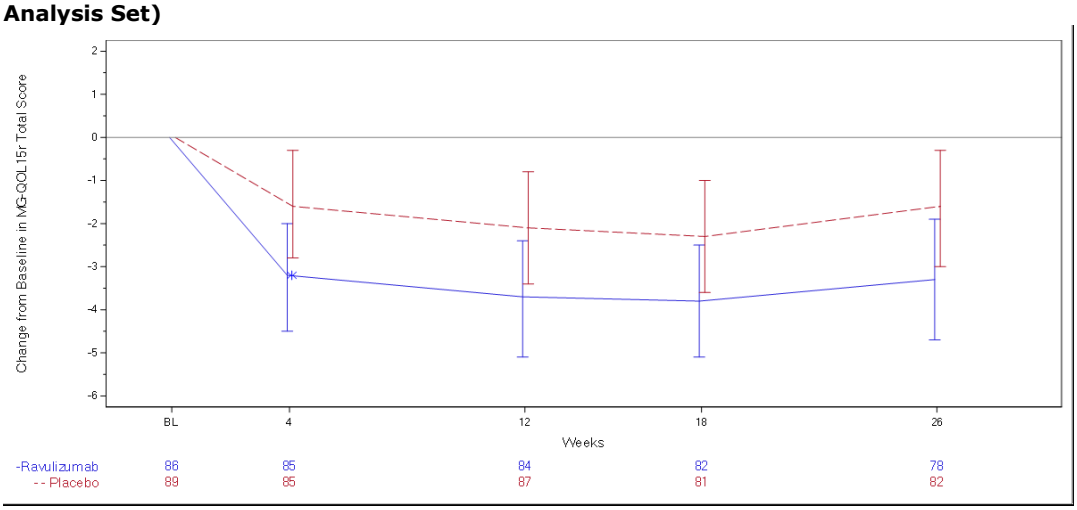



Note: Baseline was defined as the last available assessment value prior to first study drug infusion. In the event that cholinesterase inhibitor was not withheld for at least 10 hours prior to administration of the QMG assessment, the Screening visit assessment was used as Baseline. Estimates are based on a GLMM that includes treatment group, stratification factor region and QMG total score at baseline, study visit and study visit by treatment group interaction. An unstructured covariance structure was used. Abbreviations: GLMM = generalized linear mixed model; QMG = Quantitative Myasthenia Gravis score for disease severity

Although not statistically significant (p = 0.0636), the LS mean (SEM) reductions from Baseline to Week 26 in MG-QoL15r total score and Neuro-QoL Fatigue score were numerically greater in the ravulizumab group than in the placebo group during the Randomized-Controlled Period. The improvements from Baseline at each study visit were greater in the ravulizumab group than the placebo group through 26 weeks.

MG-QoL15r Total Score

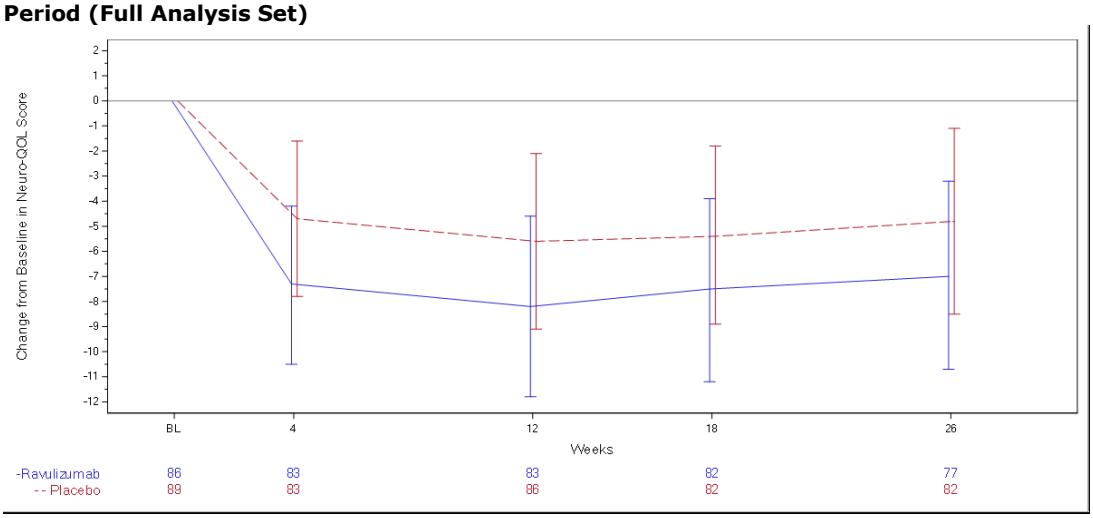
**Figure 13: Change from Baseline in the MG-QoL15r Score During the Randomized-Controlled Period (Full Analysis Set)**




Note: Baseline was defined as the last available assessment value prior to first study drug infusion. Estimates were based on MMRM that includes treatment group, stratification factor region and MG-QoL15r score at baseline, study visit, and study visit by treatment group interaction. P-values were for the comparison of treatment groups in change from baseline. An unstructured covariance structure was used.
* = p<0.05 represents a 2-sided nominal p-value.
Abbreviations: BL = Baseline; MG-QoL15r = Revised 15-Component Myasthenia Gravis Quality of Life; MMRM = mixed-effect model for repeated measure

Neuro-QoL Fatigue Score

**Figure 14: Change from Baseline in Neuro-QoL Fatigue Total Score During the Randomized-Controlled Period (Full Analysis Set)**

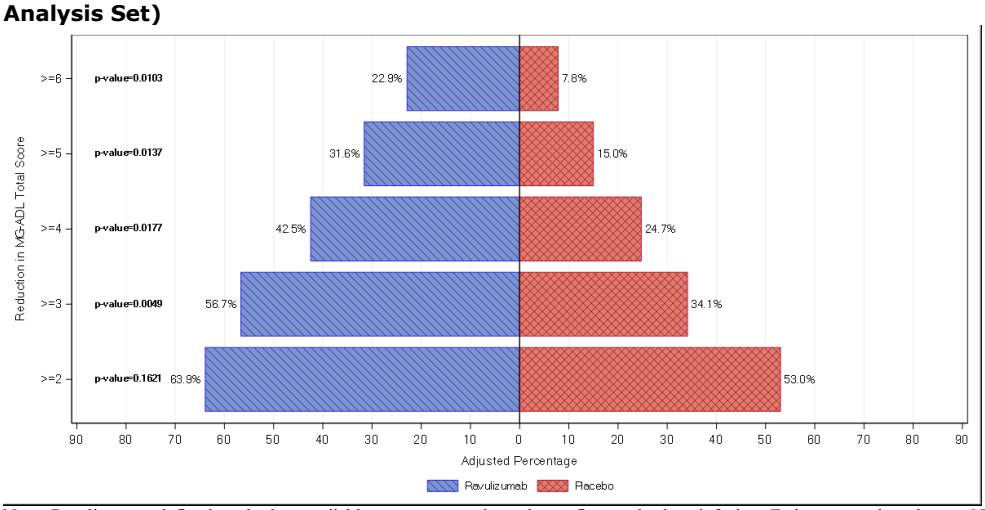



Note: Baseline was defined as the last available assessment value prior to first study drug infusion. Estimates were based on MMRM that included treatment group, stratification factor region and Neuro-QoL Fatigue score at baseline, study visit and study visit by treatment group interaction. An unstructured covariance structure was used.
Abbreviations: BL = Baseline; MMRM = mixed-effect model for repeated measures; Neuro-QoL = Neurological Quality of Life

MG-ADL 3-point Response

There was a larger proportion of clinical responders in the ravulizumab group than in the placebo group based on a ≥ 3-point reduction in MG-ADL total score from Baseline to Week 26 (OR: 2.526; 95% CI: 1.330, 4.799; nominal p = 0.0049) during the Randomized-Controlled Period.

**Figure 15: Proportion of Patients with Various Point Reductions in MG-ADL Total Score at Week 26 (Full Analysis Set)**




Note: Baseline was defined as the last available assessment value prior to first study drug infusion. Estimates are based on a GLMM that includes treatment group, stratification factor region and MG-ADL total score at baseline, study visit, and study visit by treatment group interaction. An unstructured covariance structure was used.
Abbreviations: GLMM = generalized linear mixed model; MG-ADL = Myasthenia Gravis Activities of Daily Living

***Exploratory Endpoints (Randomized-Controlled Period)***

Myasthenia Gravis Composite (MGC) score

The LS mean (SEM) reduction from Baseline to Week 26 in Myasthenia Gravis Composite (MGC) score was significantly greater in the ravulizumab group (-6.1 [0.73]) compared to the placebo group (-3.2 [0.71]) during the Randomized-Controlled Period (mean treatment difference: -2.9 [0.93]; 95% CI: -4.8, -1.1; p = 0.0019).

EQ-5D-5L VAS and Health State Index

The LS mean (SEM) change from Baseline to Week 26 in European Quality of Life Health 5-item questionnaire dimensions 5-level (EQ-5D-5L) Visual Analog Scale (VAS) was 4.0 (2.12) in the ravulizumab group and 2.7 (2.07) in the placebo group during the Randomized-Controlled Period (mean treatment difference: 1.3 [2.69]; 95% CI: -4.0, 6.6; p = 0.6374)

MG-ADL Subcomponent

The LS mean (SEM) reduction from Baseline to Week 26 in MG-ADL subcomponents was significantly greater in the ravulizumab group compared to the placebo group for respiratory score (p = 0.0484) and ocular score (p = 0.0028). Although not statistically significant at Week 26, the LS mean (SEM) reduction from Baseline to Week 26 for bulbar score and limbs score were numerically greater in the ravulizumab group compared to the placebo group at Week 26.

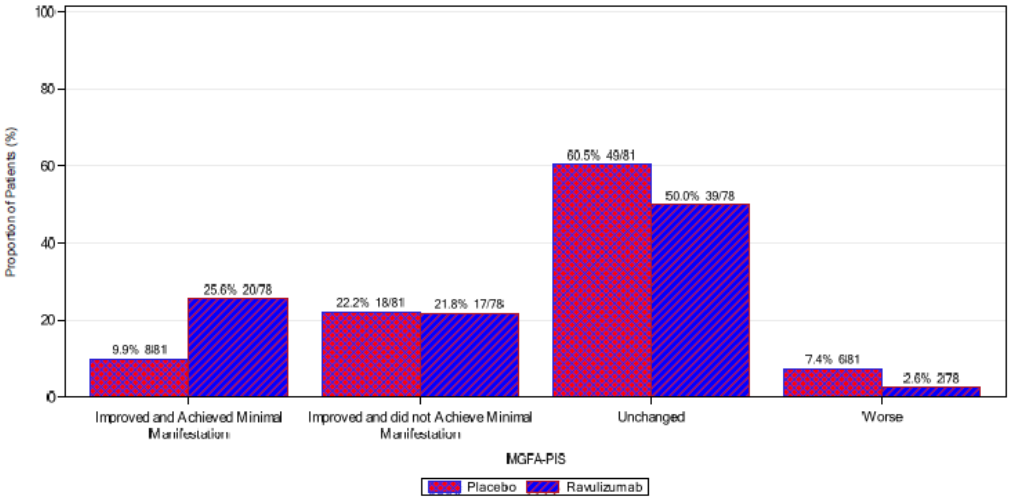
QMG Subcomponent

The LS mean (SEM) change from Baseline to Week 26 in QMG subcomponents were significantly greater in the ravulizumab group compared to the placebo group for limbs score (p = 0.0134) and ocular score (p = 0.0020). Although not statistically significant at Week 26, the LS mean (SEM) change from Baseline to Week 26 in QMG subcomponents of bulbar score was numerically greater in the ravulizumab group compared to the placebo group at Week 26. The LS mean (SEM) change from Baseline to Week 26 in QMG subcomponents of respiratory score was not greater in the ravulizumab group compared to the placebo group at Week 26.

Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS)

Patients in the ravulizumab group were more likely to achieve a status of improved and minimal manifestations than patients in the placebo group at Week 26 (OR = 2.2; 95% CI = 1.2, 4.1; p = 0.0102).

**Figure 16: Proportion of Patients in Each Category of the Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) at Week 26 (Full Analysis Set)**




Note: Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) is in comparison to pre-treatment assessment

Hospitalizations

During the Randomized-Controlled Period, the number of patients with all-cause hospitalization was similar between ravulizumab and placebo groups. Most patients were hospitalized due to non-MG related causes.

**Table 28: Hospitalizations During the Randomized-Controlled Period (Full Analysis Set)**

| Variable | Placebo (N = 89) | Ravulizumab (N = 86) |
|---|---|---|
| Number of patients hospitalized during the Randomized-Controlled Period, n (%) | 19 (21) | 16 (19) |
| MG related hospitalizations | 7 (8) | 3 (3) |
| Hospitalizations for study drug administration | 4 (4) | 1 (1) |
| Non-MG related hospitalizations | 12 (13) | 15 (17) |
| Total number of all-cause hospitalizations | 21 | 23 |
| MG-related hospitalizations | 9 | 4 |
| Total number of hospitalizations for study drug administration | 5 | 2 |
| Non-MG related hospitalizations | 12 | 19 |
| Number of patients with pre-planned hospitalization during the Randomized-Controlled Period, n (%) | 6 (6.7) | 2 (2.3) |
| Total number of pre-planned hospitalizations | 7 | 3 |

Clinical Deteriorations and Rescue Therapies

More patients in the placebo group compared to patients in the ravulizumab group reported clinical deterioration that met protocol criteria (placebo: 16.9%; ravulizumab: 9.3%) and required rescue therapy for events of clinical deterioration (placebo: 15.7%; ravulizumab: 9.3%).

**Table 29: Clinical Deteriorations During the Randomized-Controlled Period (Full Analysis Set)**

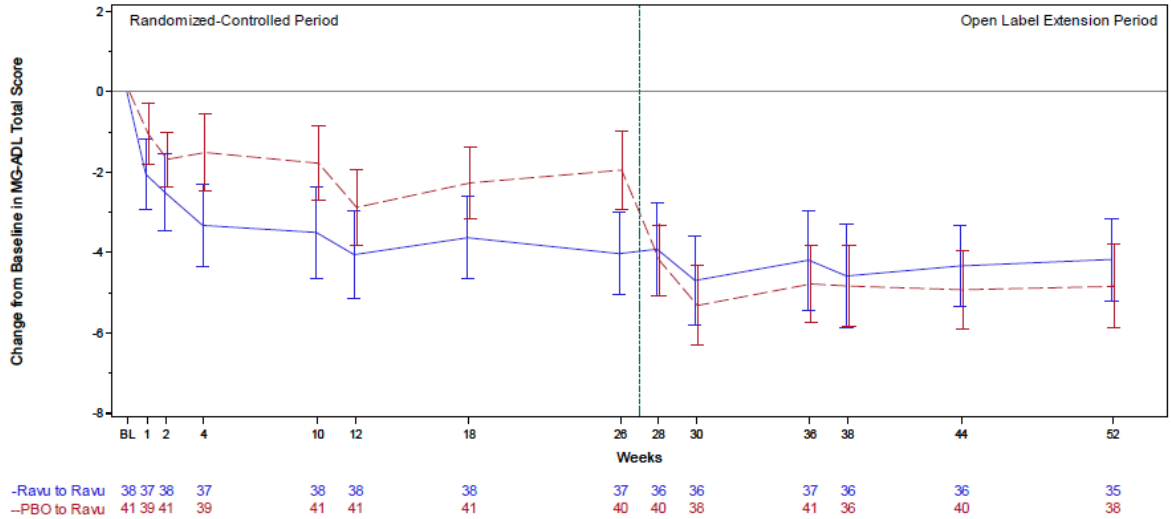
| Variable | Placebo (N = 89) | Ravulizumab (N = 86) |
|---|---|---|
| Total number of patients reporting clinical deterioration during Randomized-Controlled Period, n (%) | 18 (20.2) | 10 (11.6) |
| Total number of clinical deteriorations during Randomized-Controlled Period, n | 30 | 15 |
| Total number of patients reporting clinical deterioration as per protocol criteria during Randomized-Controlled Period, n (%) | 15 (16.9) | 8 (9.3) |
| MG crisis | 1 (1.1) | 0 |
| Significant symptomatic worsening | 5 (5.6) | 1 (1.2)[a] |
| Rescue therapy, for health in jeopardy | 12 (13.5) | 7 (8.1) |
| Total number of clinical deterioration as per protocol criteria during Randomized-Controlled Period, n | 26 | 10 |
| MG crisis | 1 | 0 |
| Significant symptomatic worsening | 6 | 1 |
| Rescue therapy, for health in jeopardy | 19 | 9 |
| Total number of patients requiring rescue therapy, n (%) | 14 (15.7) | 8 (9.3) |
| High dose corticosteroids | 1 (1.1) | 1 (1.2) |
| Plasmapheresis/plasma exchange | 1 (1.1) | 2 (2.3) |
| IVIg | 12 (13.5) | 5 (5.8) |
| Total number of clinical deterioration events requiring rescue therapy, n | 24 | 10 |
| High dose corticosteroids | 1 | 1 |
| Plasmapheresis/plasma exchange | 4 | 2 |
| IVIg | 19 | 7 |

***Other Efficacy Endpoints (Open-Label Extension)***

During the Open-Label Extension Period, a rapid and sustained improvement was observed in the PBO/RAV group while a sustained response was observed from Week 26 though Week 52 in the RAV/RAV group in MG-ADL total score, QMG total score, MG-QOL 15r total score and Neuro-QoL Fatigue score.

MG-ADL Total Score

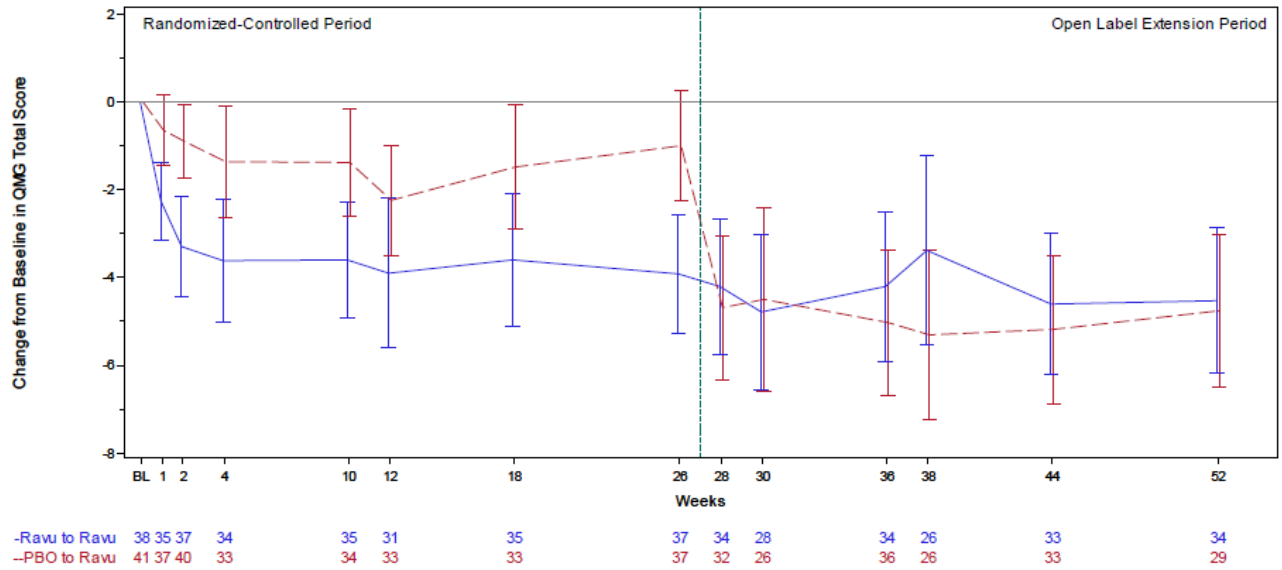
**Figure 17: Change from Randomized-Controlled Period Baseline in MG-ADL Total Score Through Week 52 (Open-Label Extension Set)**




Note: Randomized-Controlled Period Baseline was defined as the last available assessment value prior to first study drug infusion. Week 26 represented the start of the Open-Label Extension Period. Patients in the placebo group received placebo before Week 26 and received ravulizumab since Week 26. The Open-Label Extension Set consisted of all patients who received at least 1 dose ravulizumab in the Open-Label Extension Period. Per scope, only patients reaching Week 52 or withdrew prior to Week 52 by the time of data cutoff were included.
Abbreviations: BL = Baseline; MG-ADL = Myasthenia Gravis-Activities of Daily Living; PBO = placebo; Ravu = ravulizumab

## QMG Total Score

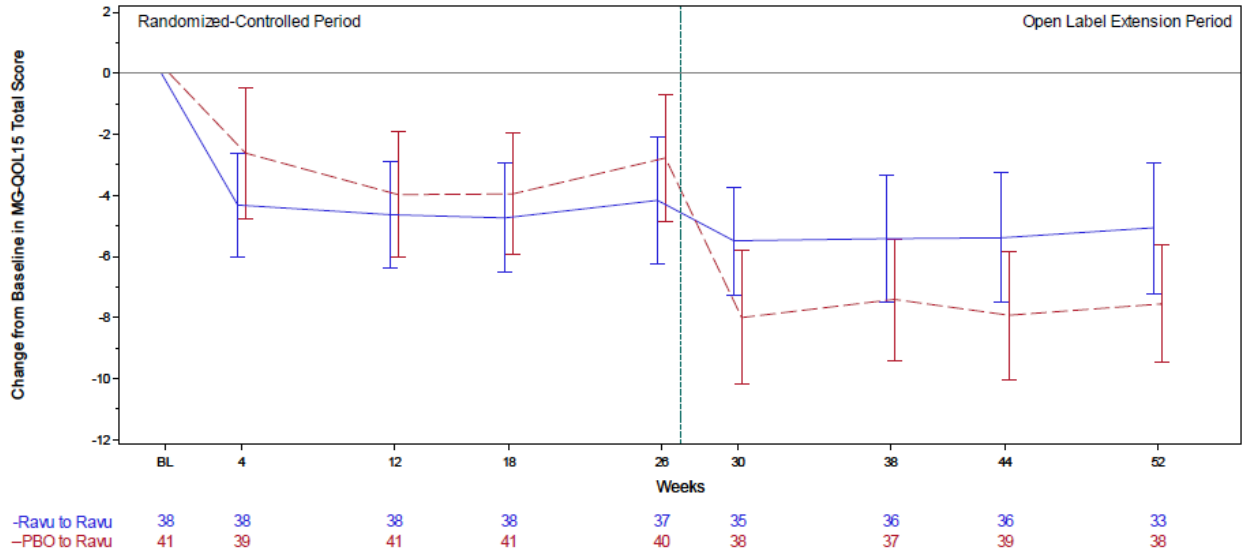
**Figure 18: Change from Randomized-Controlled Period Baseline in QMG Total Score Through Week 52 (Open-Label Extension Set)**




Note: Randomized-Controlled Period Baseline was defined as the last available assessment value prior to first study drug infusion. In the event that cholinesterase inhibitor was not withheld for at least 10 hours prior to administration of the QMG assessment, the Screening visit assessment was used as Baseline. Week 26 represented the start of the Open-Label Extension Period. Patients in the placebo group received placebo before Week 26 and received ravulizumab since Week 26.
Abbreviations: BL = Baseline; QMG = Quantitative Myasthenia Gravis; PBO = placebo; Ravu = ravulizumab

MG-QoL15r Total Score

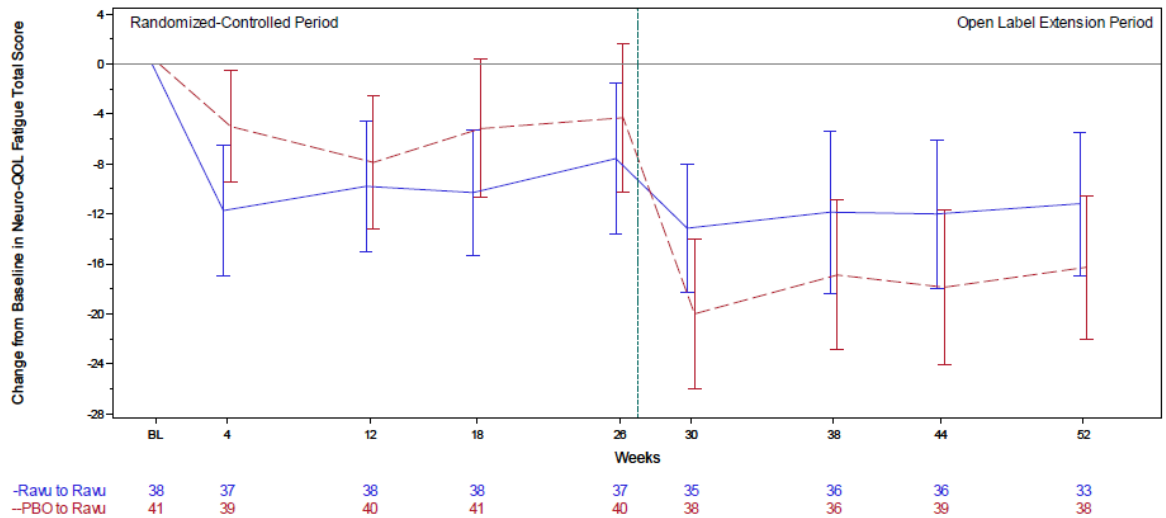
**Figure 19: Change from Randomized-Controlled Period Baseline in MG-QoL15r Score Through Week 52 (Open-Label Extension Set)**




Note: Randomized-Controlled Period Baseline was defined as the last available assessment value prior to first study drug infusion. Week 26 represented the start of the Open-Label Extension Period. Patients in the placebo group received placebo before Week 26 and received ravulizumab since Week 26. The Open-Label Extension Set consists of all patients who received at least 1 dose ravulizumab in the Open-Label Extension Period. Per scope, only patients reaching Week 52 or withdrew prior to Week 52 by the time of data cutoff were included.
Abbreviations: BL = Baseline; MG-QoL15r = Revised 15-Component Myasthenia Gravis Quality of Life; PBO = placebo; Ravu = ravulizumab

Neuro-QoL Fatigue Score

**Figure 20: Change from Randomized-Controlled Period Baseline in Neuro-QoL Fatigue Score Through Week 52 (Open-Label Extension Set)**




Note: Randomized-Controlled Period Baseline was defined as the last available assessment value prior to first study drug infusion. Week 26 represented the start of the Open-Label Extension Period. Patients in the placebo group received placebo before Week 26 and received ravulizumab since Week 26. The Open-Label Extension Set consisted of all patients who received at least 1 dose ravulizumab in the Open-Label Extension Period. Per scope, only patients reaching Week 52 or withdrew prior to Week 52 by the time of data cutoff were included.
Abbreviations: BL = Baseline; Neuro-QoL = Neurological Quality of Life; PBO = placebo; Ravu = ravulizumab

**Updated Study ALXN1210-MG-306 results**

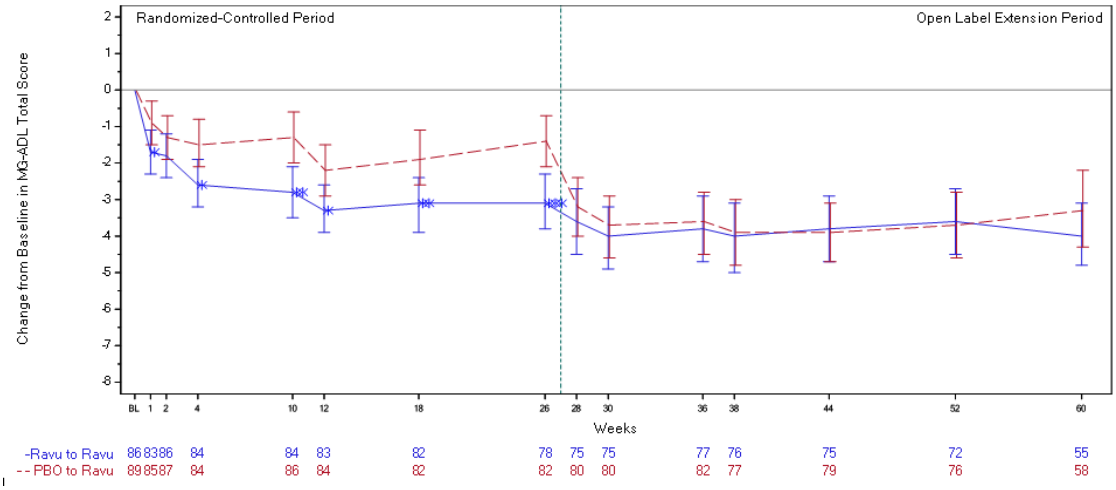
A CSR addendum was produced to provide further information for the 161 patients who received 1 or more doses of ravulizumab in the Open-Label Extension Period. Data available through 09 Nov 2021 for those 161 patients demonstrate that clinically meaningful impacts in patients with generalized myasthenia gravis (gMG) are maintained through at least 60 weeks of ravulizumab treatment. This updated analysis represents 141.6 patient-years of ravulizumab exposure.

While all patients who entered the Open-Label Extension Period received ravulizumab, patients randomized to the ravulizumab group also received 26 weeks of ravulizumab treatment during the Randomized-Controlled Period (RAV/RAV group). Patients randomized to receive placebo during the Randomized-Controlled Period had their first dose of ravulizumab at the start of the Open-Label Extension Period (Day 183 Visit) (PBO/RAV group).

Myasthenia Gravis-Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG)

Improvement in the MG-ADL total score observed during the Randomized-Controlled Period in the RAV/RAV group was sustained from Week 26 through Week 60 during the Open-Label Extension Period (least squares [LS] mean change at Week 60; -4.0 [95% confidence interval [CI]-4.8, -3.1]). During the Open-Label Extension Period, a rapid and sustained improvement of a similar magnitude to that in the RAV/RAV group during the Randomized-Controlled Period for MG-ADL total score through Week 60 was observed in the PBO/RAV group (LS mean change at Week 28: -3.2 [95% CI -4.0, -2.4]; LS mean change at Week 60 (-3.3 [95% CI -4.3, -2.2]).

**Figure 21: Change from Randomized-Controlled Period Baseline in MG-ADL Total Score (LS Mean and 95% CI) Through Week 60**

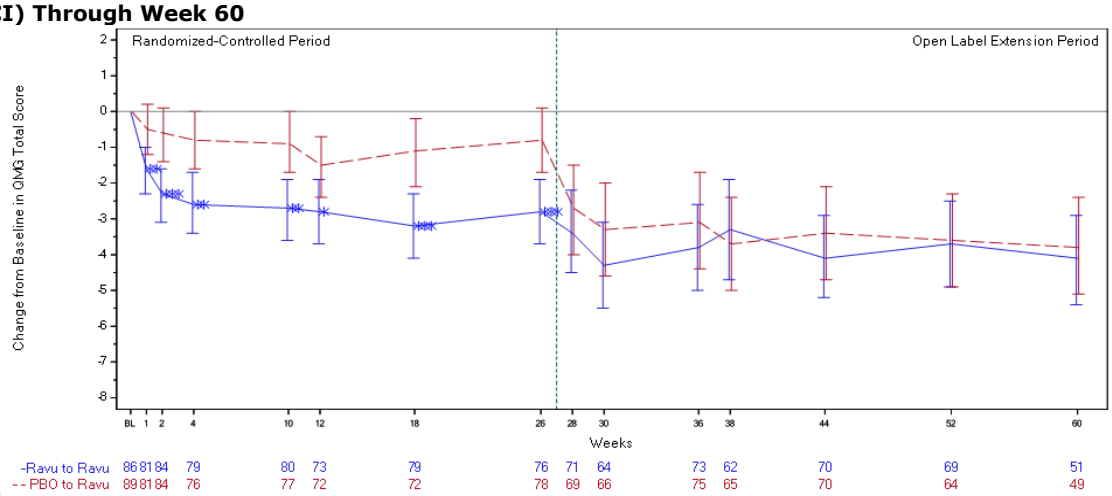



Note: Randomized-Controlled Period Baseline was defined as the last available assessment value prior to first study drug infusion in the Randomized-Controlled Period. Week 26 represented the start of the Open-Label Extension Period. The Randomized-Controlled Period estimates are based on MMRM that includes treatment group, stratification factor region, baseline score, study visit, and study visit by treatment group interaction. Visits up to Week 26 were included in the model. The Open-Label Extension Period estimates are based on MMRM that includes stratification factor region, baseline score, and study visit. A model was fit for the ravulizumab and placebo of the Open-label Extension Set separately. Data up to Week 60 at data cut-off are included.
*, **, and *** represent two-sided nominal p-value is less than 0.05, 0.01 and 0.001 for the comparison of treatment groups in change from baseline during the Randomized-Controlled Period.
Abbreviations: CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis-Activities of Daily Living; MMRM = mixed-effect model for repeated measures; PBO/RAV = placebo/ravulizumab; RAV/RAV = ravulizumab/ravulizumab

Improvement in the QMG total score observed during the Randomized-Controlled Period in the RAV/RAV group was sustained from Week 26 through Week 60 during the Open-Label Extension Period

(LS mean change at Week 60: -4.1 [95% CI -5.4, -2.9]). During the Open-Label Extension Period, a rapid and sustained improvement of a similar magnitude to that in the RAV/RAV group during the Randomized-Controlled Period for QMG total score through Week 60 was observed in the PBO/RAV group (LS mean change at Week 28: -2.7 [95% CI -4.0, -1.5]; LS mean change at Week 60 (-3.8 [95% CI -5.1, -2.4])

**Figure 22: Change from Randomized-Controlled Period Baseline in QMG Total Score (LS Mean and 95% CI) Through Week 60**

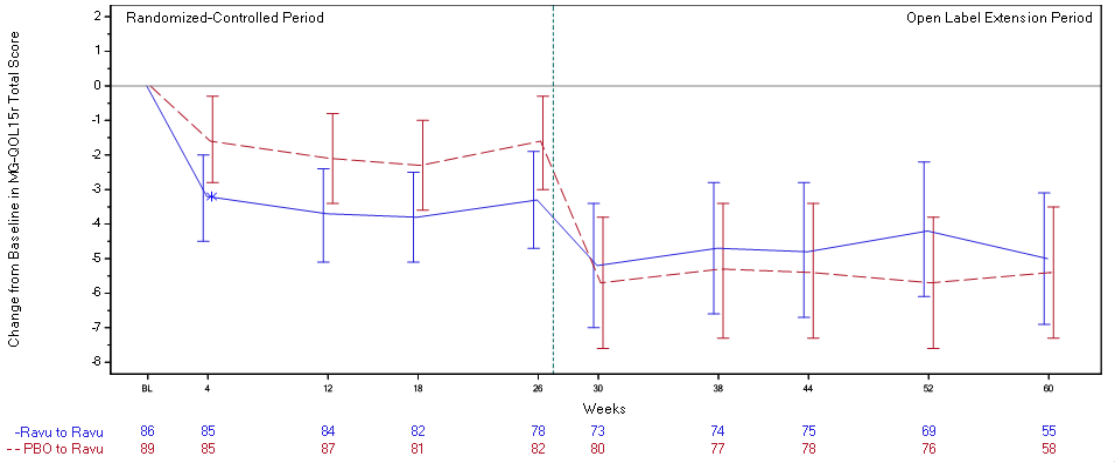



Note: Randomized-Controlled Period Baseline was defined as the last available assessment value prior to first study drug infusion in the Randomized-Controlled Period Baseline. Week 26 represented the start of the Open-Label Extension Period. The Randomized-Controlled Period estimates are based on MMRM that includes treatment group, stratification factor region, baseline score, study visit, and study visit by treatment group interaction. Visits up to Week 26 were included in the model. The Open-Label Extension Period estimates are based on MMRM that includes stratification factor region, baseline score, and study visit. A model was fit for the ravulizumab and placebo of the Open-label Extension Set separately. Data up to Week 60 at data cut-off are included.
*, **, and *** represent two-sided nominal p-value is less than 0.05, 0.01 and 0.001 for the comparison of treatment groups in change from baseline during the Randomized-Controlled Period.
Abbreviations: CI = confidence interval; LS = least squares; MMRM = mixed-effect model for repeated measures; PBO/RAV = placebo/ravulizumab; QMG = Quantitative Myasthenia Gravis; RAV/RAV = ravulizumab/ravulizumab

Other Myasthenia Gravis (MG)-Related Outcomes

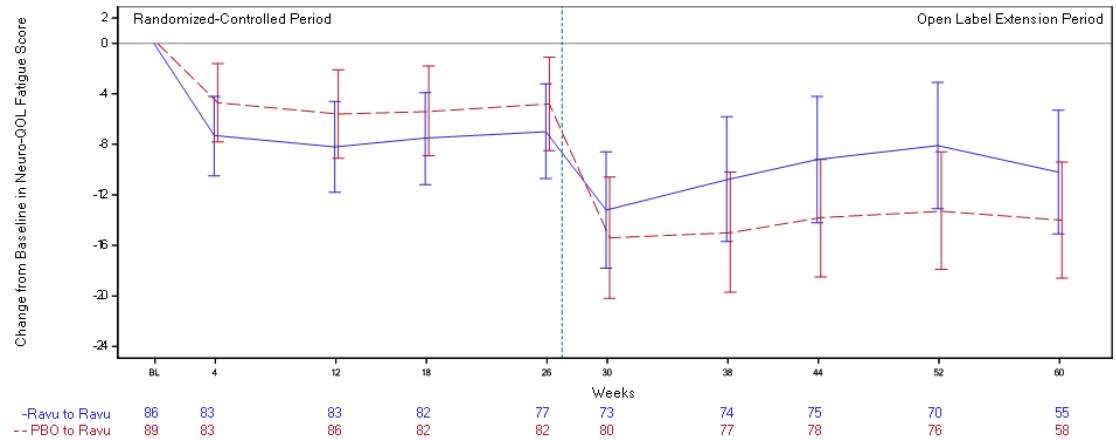
Although the change from baseline compared to placebo was not statistically significant at Week 26 of the Randomized-Controlled Period, similar trends favouring ravulizumab were observed for the secondary endpoints of Revised Myasthenia Gravis Quality of Life 15-item scale total score (Figure 23) and the Neurological Quality of Life fatigue score (Figure 24) improvement which was continued up to Week 60.

**Figure 23: Change from Randomized-Controlled Period Baseline in MG-QoL15r Score (LS Mean and 95% CI) Through Week 60**




Note: Randomized-Controlled Period Baseline was defined as the last available assessment value prior to first study drug infusion in the Randomized-Controlled Period Baseline. Week 26 represented the start of the Open-Label Extension Period. The Randomized-Controlled Period estimates are based on MMRM that includes treatment group, stratification factor region, baseline score, study visit, and study visit by treatment group interaction. Visits up to Week 26 were included in the model. The Open-Label Extension Period estimates are based on MMRM that includes stratification factor region, baseline score, and study visit. A model was fit for the ravulizumab and placebo of the Open-label Extension Set separately. Data up to Week 60 at data cut-off are included.
* represents two-sided nominal p-value is less than 0.05 for the comparison of treatment groups in change from baseline during the Randomized-Controlled Period.
Abbreviations: CI = confidence interval; LS = least squares; MG-QoL15r = revised Myasthenia Gravis Quality of Life 15-item scale; MMRM = mixed-effect model for repeated measures; PBO/RAV = placebo/ravulizumab; RAV/RAV = ravulizumab/ravulizumab
Source: ALXN1210-MG-306 Week 60 CSR Addendum Figure 14.2.2.3.2.3.5

**Figure 24: Change from Randomized-Controlled Period Baseline in Neuro-QoL Fatigue Score (LS Mean and 95% CI) Through Week 60**




Note: Randomized-Controlled Period Baseline was defined as the last available assessment value prior to first study drug infusion in the Randomized-Controlled Period Baseline. Week 26 represented the start of the Open-Label Extension Period. The Randomized-Controlled Period estimates are based on MMRM that includes treatment group, stratification factor region, baseline score, study visit, and study visit by treatment group interaction. Visits up to Week 26 were included in the model. The Open-Label Extension Period estimates are based on MMRM that includes stratification factor region, baseline score, and study visit. A model was fit for the ravulizumab and placebo of the Open-label Extension Set separately. Data up to Week 60 at data cut-off are included.
Abbreviations: CI = confidence interval; LS = least squares; MMRM = mixed-effect model for repeated measures; Neuro-QoL = Neurological Quality of Life; PBO/RAV = placebo/ravulizumab; RAV/RAV = ravulizumab/ravulizumab

During the Open-Label Extension Period of the study when immunosuppressant therapy (IST) dose adjustments were permitted per protocol, 47.8% of patients reported a change in their IST usage. The most common change was a decrease in corticosteroids (28.0%), with the most common reason for

decrease being improvement in MG symptoms (21.7%), which further supports the efficacy of ravulizumab in patients with gMG.

Estimated Completion Date

The estimated completion date when the last patient will exit Study ALXN1210-MG-306 is planned to occur by 31 Dec 2023.

## Ancillary analyses

### Subgroup Analysis

Subgroup analyses were based on the following categories (Table 30):

**Table 30: Defined Subgroups**

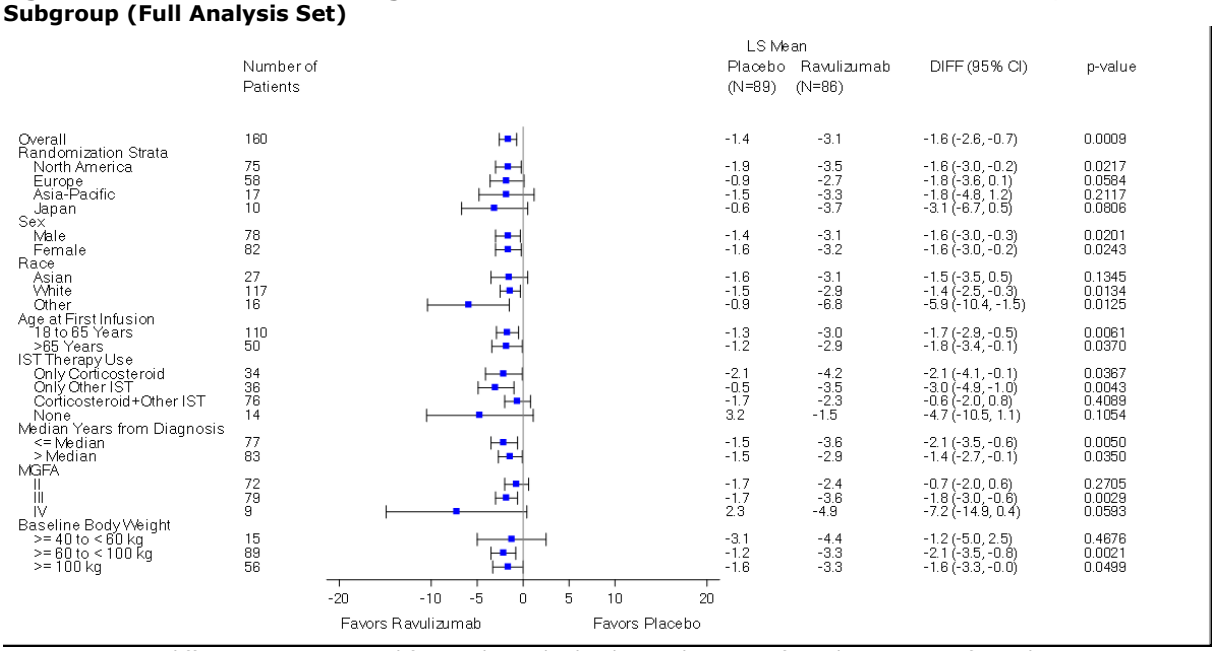
| Subgroup | Categories |
|---|---|
| Geographic regiona | Asia-Pacific; Europe; Japan; North America |
| Sex | Male; female |
| Race | Asian; Other; White |
| Age at first study drug infusion | 18 to 65 years; > 65 years |
| IST use at baseline | Corticosteroid; corticosteroid + IST; IST; none |
| Years from diagnosis to informed consent | ≤ median; > median |
| Baseline MGFA Clinical Classification | II; III; IV |
| Baseline body weight | ≥ 40 to < 60 kg; ≥ 60 to < 100 kg; ≥ 100 kg |

a North America included USA and Canada; Asia-Pacific included only South Korea
Abbreviations: IST = immunosuppressive therapy; MGFA = Myasthenia Gravis Foundation of America

MG-ADL Total Score

No sensitive subgroups were identified for MG-ADL total score. The point estimates for all groups favoured ravulizumab (Figure 25).

**Figure 25: Forest Plot of Change from Baseline to Week 26 in MG-ADL Total Score, Overall and by Subgroup (Full Analysis Set)**

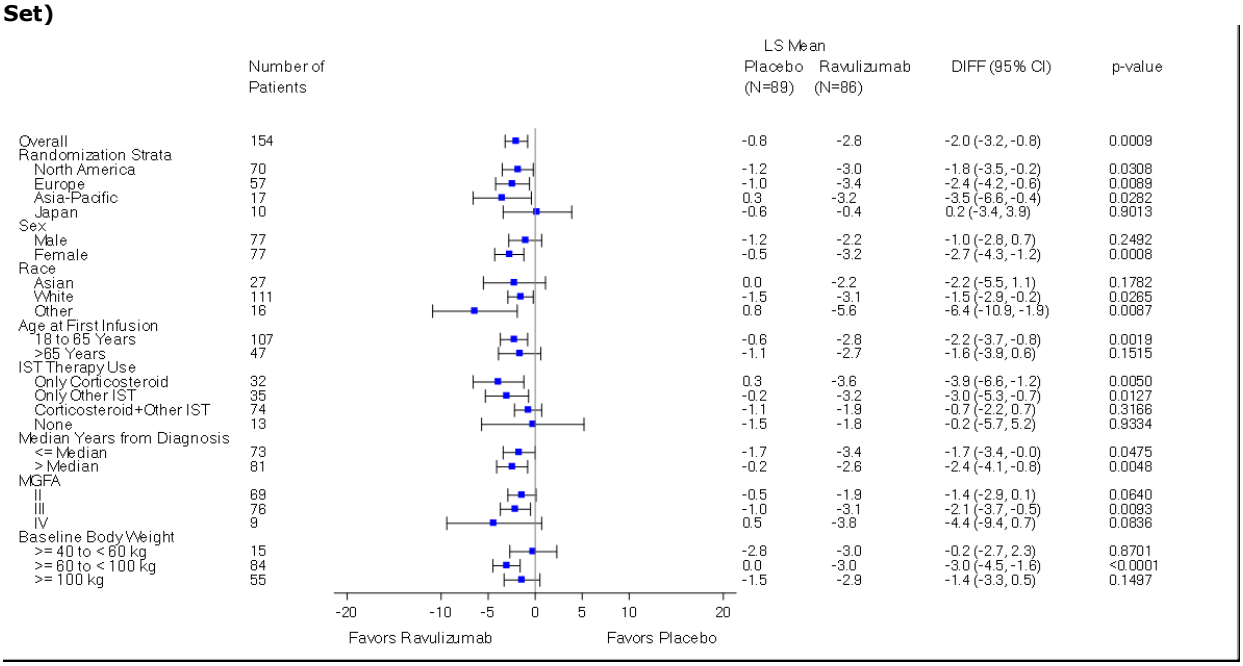



Note: Treatment difference was estimated for ravulizumab-placebo. Median years from diagnosis to informed consent was 6.5.
Abbreviations: CI = confidence interval; DIFF = difference; IST = immunosuppressant therapy; LS = least square; MG-ADL = Myasthenia Gravis-Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America

QMG Total Score

No sensitive subgroups were identified for QMG total score. The point estimates for most groups favored ravulizumab (Figure 26).

**Figure 26: Forest Plot of Change from Baseline to Week 26 in QMG, Overall and by Subgroup (Full Analysis Set)**




Note: Treatment difference was estimated for ravulizumab-placebo. Median years from diagnosis to informed consent was 6.5.
Abbreviations: CI = confidence interval; DIFF = difference; IST = immunosuppressant therapy; LS = least square; MGFA = Myasthenia Gravis Foundation of America; QMG = Quantitative Myasthenia Gravis

## *Summary of main study*

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 31 - Summary of Efficacy for trial ALXN1210-MG-306**

| **Title: 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 Myasthenia Gravis** | | |
|---|---|---|
| Study identifier | ALXN1210-MG-306, EudraCT number 2018-003243-39, NCT03920293 | |
| Design | Randomized, double-blind, placebo-controlled multicenter study | |
| | Duration of main phase: | 26 weeks |
| | Duration of screening phase: | Up to 4 weeks |
| | Duration of extension phase: | Up to 2 years |
| Hypothesis | Superiority | |

| | | | |
|---|---|---|---|
| Treatments groups | Ravulizumab | | Ravulizumab IV body weight-based loading dose on Day 1, followed by maintenance doses on Day 15 and every 8 weeks therafter<br>N = 86 patients |
| | Placebo | | Matching treatment<br>N = 89 patients |
| Endpoints and definitions | Primary endpoint | MG-ADL total score | Change from Baseline in MG-ADL total score at Week 26 was analyzed using MMRM |
| | Secondary endpoint | QMG total score | Change from Baseline in QMG total score at Week 26 was analyzed using MMRM. |
| | Secondary endpoint | QMG responder rate | Improvement of at least 5 points in the QMG total score from Baseline at Week 26. |
| | Secondary endpoint | MG-QoL15r score | Change from Baseline in MG-QoL15r score at Week 26 was analyzed using MMRM. |
| | Secondary endpoint | Neuro-QoL Fatigue score | Change from Baseline in Neuro-QoL Fatigue score at Week 26 was analyzed using MMRM. |
| | Secondary endpoint | MG-ADL responder rate | Improvement of at least 3 points in the MG-ADL total score from Baseline at Week 26. |
| Database lock | 30 Jun 2021 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis: Change from Baseline in MG-ADL total score at Week 26 was analyzed using MMRM** | | |
| Analysis population and time point description | Intent to treat (all randomized patients who received at least 1 dose of study drug)<br>Week 26<br>Week 26 | | |
| Descriptive statistics and estimate variability | Treatment group | Ravulizumab | Placebo |
| | Number of subject | 86 | 89 |
| | Mean change from Baseline in MG-ADL total score at Week 26 | -3.1 | -1.4 |
| | 95% confidence interval | -3.8, -2.3 | -2.1, -0.7 |
| Effect estimate per comparison | Primary endpoint: Change from Baseline in MG-ADL total score at Week 26 | Comparison groups | Ravulizumab and placebo |
| | | Difference between groups | -1.6 |
| | | Confidence interval | -2.6, -0.7 |
| | | P-value using REML based MMRM | 0.0009 |
| **Analysis description** | **Secondary analysis: Change from Baseline in QMG total score at Week 26 was analyzed using MMRM.** | | |
| Analysis population and time point description | Intent to treat (all randomized patients who received at least 1 dose of study drug)<br>Week 26 | | |
| | Treatment group | Ravulizumab | Placebo |

| | | | |
|---|---|---|---|
| Descriptive statistics and estimate variability | Number of subject | 86 | 89 |
| | Change from Baseline in QMG total score at Week 26 | -2.8 | -0.8 |
| | Confidence interval | -3.7, -1.9 | -1.7, 0.1 |
| Effect estimate per comparison | Change from Baseline in QMG total score at Week 26 | Comparison groups | Ravulizumab and placebo |
| | | Difference between groups | -2.0 |
| | | 95% confidence interval | -3.2, -0.8 |
| | | P-value using REML based MMRM | 0.0009 |
| **Analysis description** | **Secondary analysis: Improvement of at least 5 points in the QMG total score from Baseline at Week 26.** | | |
| Analysis population and time point description | Intent to treat (all randomized patients who received at least 1 dose of study drug)<br>Week 26 | | |
| Descriptive statistics and estimate variability | Treatment group | Ravulizumab | Placebo |
| | Number of subject | 86 | 89 |
| | QMG ≥5-point improvement | 30.0% | 11.3% |
| | Confidence interval | 19.2, 43.5 | 5.6, 21.5 |
| Effect estimate per comparison | Change from Baseline in QMG total score at Week 26 | Comparison groups | Ravulizumab and placebo |
| | | Odds ratio | 3.350 |
| | | 95% confidence interval | 1.443, 7.777 |
| | | P-value using REML based MMRM | 0.0052 |
| **Analysis description** | **Secondary analysis: Change from Baseline in MG-QoL15r score at Week 26 was analyzed using MMRM.** | | |
| Analysis population and time point description | Intent to treat (all randomized patients who received at least 1 dose of study drug)<br>Week 26 | | |
| Descriptive statistics and estimate variability | Treatment group | Ravulizumab | Placebo |
| | Number of subject | 86 | 89 |
| | Change from Baseline in QMG total score at Week 26 | -3.3 | -1.6 |
| | Confidence interval | -4.7, -1.9 | -3.0, -0.3 |
| Effect estimate per comparison | MG-QOL15r | Comparison groups | Ravulizumab and placebo |
| | | Difference between groups | -1.7 |
| | | 95% confidence interval | -3.4, 0.1 |

| | | | |
|---|---|---|---|
| | | P-value using REML based MMRM | 0.0636 |
| **Analysis description** | **Secondary analysis: Change from Baseline in Neuro-QoL Fatigue score at Week 26 was analyzed using MMRM.** | | |
| Analysis population and time point description | Intent to treat (all randomized patients who received at least 1 dose of study drug)<br>Week 26 | | |
| Descriptive statistics and estimate variability | Treatment group | Ravulizumab | Placebo |
| | Number of subject | 86 | 89 |
| | Neuro-QOL-fatigue | -7.0 | -4.8 |
| | Confidence interval | -10.7, -3.2 | -8.5, -1.1 |
| Effect estimate per comparison | Change from Baseline in QMG total score at Week 26 | Comparison groups | Ravulizumab and placebo |
| | | Difference between groups | -2.2 |
| | | 95% confidence interval | -6.9, 2.6 |
| | | P-value using REML based MMRM | 0.3734* |
| Notes | * Nominal p-values | | |
| **Analysis description** | **Secondary analysis: Improvement of at least 3 points in the MG-ADL total score from Baseline at Week 26.** | | |
| Analysis population and time point description | Intent to treat (all randomized patients who received at least 1 dose of study drug)<br>Week 26 | | |
| Descriptive statistics and estimate variability | Treatment group | Ravulizumab | Placebo |
| | Number of subject | 86 | 89 |
| | MG-ADL ≥3-point improvement* | 56.7% | 34.1% |
| | Confidence interval | 44.3, 68.3 | 23.8, 46.1 |
| Effect estimate per comparison | Improvement of at least 3 points in the MG-ADL total score from Baseline at Week 26 | Comparison groups | Ravulizumab and placebo |
| | | Odds ratio | 2.526 |
| | | 95% confidence interval | 1.330 , 4.799 |
| | | P-value using REML based MMRM | 0.0049* |
| Notes | * Nominal p-values | | |

## 2.4.3. Discussion on clinical efficacy

## Design and conduct of clinical studies

The main efficacy data in support of this extension of indication application was obtained from one Phase III clinical trial (Study ALXN1210-MG-306; Study MG-306).

This submission was initially based on data from the 26-week double-blind phase (completed) and the available results from the extension phase (still ongoing) as of the first data cut-off date (11 May 2021). Additional data, was provided during the procedure, for the 161 patients who received 1 or more doses of ravulizumab in the extension period collected up to the Week 60 visit in the Open-Label Extension Period as of the data cut-off date (09 Nov 2021).

The selection criteria defined subjects with confirmed diagnosis of gMG (determined by the presence of AchR antibodies and electrophysiological/pharmacological confirmation) who were symptomatic (MG-ADL ≥6) in spite of being treated with current standard of care.

Prior or concomitant MG treatment was not a requisite at baseline which could have led to inclusion of recently diagnosed patients. However, in the study only one randomized patient was not previously treated. Patients having received recent treatment with rituximab or IVIg/PE were excluded as well as those who had been previously treated with eculizumab.

A total of 242 patients were screened, of which 175 patients were randomized (86 patients to the ravulizumab group and 89 patients to the placebo group). A total of 158 patients (90.3%) entered the Open-Label extension: 77 (89.5%) in ravulizumab arm and 81 (91.0%) in placebo arm. Only the data from 79 patients (38 patients from the ravulizumab group and 41 patients from the placebo group) who reached Week 52 by the time of the data cut-off are available for analysis. This is an important limitation for the assessment of the maintenance of the effect.

In Study MG-306 most of demographics and disease characteristics at baseline were well balanced over treatment arms and the population is considered to have been adequately selected and is as representative of the EU.

Most of the patients had moderate to severe weakness affecting muscles other than the ocular muscles (66% MGFA Class III/IV), all had received prior treatment for their condition and most of them were treated at entry with more than one MG medication. Patients presented with a mean MG-ADL total score of 9.0, and the mean QMG total score of 15.0. As such, CHMP considered that in spite of previous treatments, the patient population included in the trial showed a relevant disease burden in order to assess the effect of ravulizumab in the approved indication.

The proposed dosing regimen is based on body weight and is identical to that approved for the treatment of PHN and aHUS (for further discussion on the approved dosing regimen please refer to the discussion on clinical pharmacology above section 2.3.5). This is considered adequate by CHMP.

Patients on placebo, who entered the OLE period, received a loading dose of ravulizumab and those treated with ravulizumab in the randomized controlled period received a blinded dose of 900 mg of ravulizumab to ensure maintenance of complete complement component 5 (C5) inhibition until the next scheduled maintenance dose.

During the double-blind period ravulizumab was administered in a 10 mg/mL formulation. During the OLE period a total of 35 patients were switched to a 100 mg/mL formulation following the same dosing regimen than that received during the controlled period. The 74 patients from the US did not receive this formulation, apparently due to the lack of availability for supplying the product during the study

duration. Apart from the differences between both formulations, those regarding qualitative composition, preparation, or administration conditions were not considered clinically relevant.

With respect to the impact of COVID 19 pandemic on the conduct of the study a total of five patients (3 patients on placebo and 2 patients on ravulizumab) missed a total of 6 infusions due to COVID-19 (3 placebo patients missed 1 infusion each and 2 ravulizumab-treated patients missed 1 and 2 infusions each). Patients on ravulizumab treatment and 2 patients on placebo did not receive further doses after COVID-19 and discontinued the study. One placebo patient received a scheduled dosing. CHMP considered that since only a low number of patients missed infusions due to COVID-19 and this affected both arms in a similar way, no impact on the efficacy or safety results is expected.

Plasma exchange (PE), plasmapheresis (PP), and intravenous immunoglobulin (IVIg) have been shown to reduce ravulizumab serum levels As such, regarding the need for a supplemental dose in case of plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg additional clarifications were requested by the CHMP on whether the proposed supplemental dose resulted in comparable exposure over time. Simulations in four scenarios were performed where the rescue therapy with plasma exchange (PE), plasmapheresis (PP) or intravenous immunoglobulin (IVIg) could be potentially administered: a) immediately after the loading dose (Day 1); b) at 2 weeks after the loading dose (immediately before the first maintenance dose on Day 15); c) immediately after any maintenance dose; and d) at 8 weeks after any maintenance dose (immediately before the next maintenance dose). The body weight strata were also taken into account. The simulations performed show that the recommended supplemental doses of ravulizumab did not lead to apparent drug accumulation. Therefore, a supplemental dose of ravulizumab IV is recommended immediately after each PP or PE session or complete IVIg course. This information is appropriately reflected in section 4.2 of the Product Information (PI).

## Efficacy data and additional analyses

The evaluation of efficacy of ravulizumab focused on the assessment of the gMG signs and symptoms by the patient (MG-ADL; primary endpoint) and the physician (QMG; main secondary endpoint).

The primary endpoint was the change in MG-ADL score reported by the patient. At Week 26 ravulizumab arm showed a statistically significant reduction in MG-ADL score from baseline irrespective of rescue therapy in comparison with placebo. Patients in the ravulizumab treatment group showed a 3.1-point reduction whereas patients receiving placebo showed a 1.4-point reduction (mean difference: -1.6 [0.49]; 95% confidence interval [CI]: -2.6, -0.7; p = 0.0009).

The MG-ADL responder criterion was met in 48 (56.7%) patients in the ravulizumab group compared to 30 (34.1%) patients in the placebo group. Of note, this analysis was not considered (formally) statistically significant according to the prespecified hierarchical testing for secondary endpoints.

Main secondary endpoints assessed the effect of ravulizumab by the physician (QMG total score; QMG responder rate). A statistically significant difference was observed between ravulizumab and placebo (-2.0 [-3.2, -0.8]; p=0.009). More patients on ravulizumab showed significantly better control of the disease. 30% of patients on ravulizumab had ≥ 5 point reduction in the QMG total score compared with 11.3% placebo (OR 3.350 [95% CI 1.443, 7.777]; p=0.0052).

Of note, the efficacy analyses were conducted irrespective of the rescue therapy received by the patients in case of clinical deterioration. Additional analyses were conducted based on rescue therapy: one of them includes the change from baseline in MG-ADL total score up to the time of rescue therapy and the second excludes the 22 patients requiring rescue therapy (14 placebo- and 8 ravulizumab-treated

patients). The results do not suggest that the use of rescue therapy has had a significant impact on the response to ravulizumab.

According to the testing hierarchy, the remaining three secondary endpoints (change in MG-QOL15r score, change in Neuro-QoL fatigue scale, MG-ADL responder rate) were not considered statistically significant even if results numerically favoured ravulizumab compared to placebo.

MG Composite Scale results were in line with those observed for MG-ADL score and QMG scales. Patients treated with both ravulizumab and with placebo experienced a reduction in the scores (ravulizumab -6.1 [0.73], placebo -3.2 [0.71]). The difference was statistically significant (-2.9 [0.93]; 95% CI: -4.8, -1.1; p = 0.0019) although the clinical relevance is perceived as borderline considering the three-point reduction threshold established as clinically meaningful in the literature.

Achieving improvement with minimal manifestations of the disease was reported in 25.6% of patients in the ravulizumab group compared to 9.9% of patients in the placebo group at Week 26. More patients treated with placebo than those receiving ravulizumab suffered clinical deterioration (18 [20.2%] vs. 10 [11.6%]) or required rescue therapy (14 [15.7%] vs. 8 [9.3%]) during the study. Similarly, fewer patients on ravulizumab needed hospitalization due to MG during the 26 week period of treatment compared to placebo (7 [8%] vs. 3 [3%]).

No important differences were observed between ravulizumab and placebo in subgroups studied according region, sex, race, age, disease characteristics or body weight.

Overall, ravulizumab showed an effect over placebo on the control of symptoms assessed by the patient (MG-ADL score, primary endpoint) and by the physician (QMG score; secondary endpoint) in a population with an established condition of moderate severity in spite of concomitant MG therapy. This is consistent with the MGC score results, a scale derived from the other two scales mentioned above.

However, the clinical meaningfulness of the observed changes versus the respective established thresholds was questioned by the CHMP. CHMP considered that the fact that the analyses were performed irrespective of whether rescue therapy was used could introduce a confounding factor in the assessment of the efficacy of ravulizumab. The small (absolute) differences between groups in relevant clinical aspects such as required rescue therapy (difference 6.4%), clinical deterioration experienced (difference 8.6%) or need of hospitalization due to MG (difference 5%) additionally put into question the benefit of the product in the management of MG.

The statistically significant reduction experienced in symptoms of 1.6 points in the mean change in MG-ADL score (primary endpoint) with respect to baseline during the randomized controlled period was considered as a modest effect. This also applied to the observed findings in the main secondary endpoints when they were expressed in terms of absolute changes of the respective scales.

CHMP acknowledged that Study MG-306 included a population on IST treatment with remaining symptomatology in whom an effect may be difficult to evidence due to the limited room for improvement and the fluctuating nature of the condition.

As stated, the clinical relevance of the treatment effect could be questioned based on the fact that it did not achieve the accepted thresholds for clinical meaningfulness for the utilized scales established in literature (i.e. MCID of 2 point[22],[23]). However, it should be considered that this difference has been defined by absolute change from baseline in individual patients, and not as differences in average changes between groups[24]. In this regard these thresholds should be used for individual responder

[22] Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. Neurology. 1999;52(7):1487-9.
[23] Muppidi S, Wolfe GI, Conaway M, Burns TM. MG-ADL: still a relevant outcome measure. Muscle Nerve. 2011;44(5):727-31.
[24] Chung AS, Copay AG, Olmscheid N, Campbell D, Walker JB, Chutkan N. Minimum clinically important difference: current trends in the spine literature. Spine. 2017;42(14):1096-1105.

analyses and not as a reference point for a population-average drug-placebo treatment effect. Admittedly, this criterion could be considered as a cut-off value in responder analysis, as this is based on an "individual level" approach. In this respect 63.9% of patients treated with ravulizumab and 53.0% of patients treated with placebo showed a 2-point reduction in MG-ADL score, with the reported 10.9% difference being of difficult interpretation. Moreover, the measured difference between ravulizumab and placebo did not achieve the treatment effect of 1.9 points on the MG-ADL score used at the planning stage.

An estimation of the effect size for the primary and secondary endpoints (MG-ADL and QMG scales) was provided in order to inform about the magnitude of treatment effects, showing an Hedge's g effect size of -0.49 and -0.50, respectively, which is defined as a moderate effect.

While there are some uncertainties on the clinical relevance of the treatment effect size, the totality of the demonstrated effects has to be considered. In this respect, the CHMP considered that the observed treatment effects are consistent across the responder rates reported both from the patient's (MG-ADL) and physician's perspective (QMG). It should also be highlighted that more stringent criteria led to clearer differences between the ravulizumab and the placebo groups.

From the patient perspective (QoL measures), the changes in the MG-QOL15r score and in the Neuro-QoL fatigue scale were not statistically significant even if results numerically favoured ravulizumab compared to placebo.

Supportive evidence derives also from the clinical impact of ravulizumab in the course of the disease. Ravulizumab treated patients experienced less clinical deterioration, less MG-related hospitalization and required less rescue therapy than placebo treated patients (Table 3 above). The interpretation of these outcomes is limited by the reduced numbers of events by group and the exploratory nature of the endpoints. However, a consistent response has been shown in the scales measured, which reinforces the observed effect. During the extension period, where changes in background therapy were allowed, 50.3% of patients had a change in concomitant MG medication. The most common change was a decrease in corticosteroids for systemic use due to MG symptoms improved (20.7%) with 11 (6.5%) patients discontinuing corticosteroids for systemic use.

Whereas some uncertainties still remain (e.g., what treatment effect size with respect to placebo is to be considered clinically relevant) the totality of the data submitted supports the conclusion that efficacy has been sufficiently demonstrated in order to support the use of ravulizumab in the approved indication.

Maintenance of the effect

Maintenance of the effect of ravulizumab beyond 6 month treatment is based on the still ongoing open label period, where all patients involved in Study MG-306 are treated with ravulizumab and followed up to 2 years. An update of the Study MG-306 with a clinical database cut-off date of 09 Nov 2021 was provided during the assessment of this applicaton. Additional data from the 161 patients who received 1 or more doses of ravulizumab in the extension period collected up to the Week 60 visit in the Open-Label Extension Period was provided. All patients received treatment with ravulizumab during the Open-Label Extension Period, including patients randomized to ravulizumab and patients randomized to placebo during the Randomized-Controlled Period (RAV/RAV and PBO/RAV group, respectively). When patients who received placebo in the randomized controlled period were treated with ravulizumab in the open-label extension period an improvement similar to that achieved by patients on active treatment in the first part of the study was observed. In patients previously treated with ravulizumab, the response was maintained.

During this phase of the clinical trial background therapy could be adjusted. In this period 50.3% of patients had a change in concomitant MG medication. The most common change was a decrease in corticosteroids for systemic use due to MG symptoms improved (20.7%) with 11 (6.5%) patients discontinuing corticosteroids for systemic use.

With the limitations given by the open label design and the fact that the study is still ongoing, the maintenance of the effect was considered sufficiently established. The final results of the study will have to be submitted once available.

Ravulizumab is structurally related to eculizumab, both products providing sustained inhibition of complement component 5. It is therefore conceivable that gMG patients in treatment with eculizumab could be switched to ravulizumab seeking for more convenient administration if response is achieved. This is not the case in non-responder to eculizumab patients in whom non response to ravulizumab is likely. This information has been reflected in the SmPC.

Wording of the indication

The initial proposed indication was:

"*The treatment of adult patients with anti-acetylcholine receptor (AChR) antibody-positive generalized myasthenia gravis (gMG) with remaining symptomatology despite at least one immunomodulatory therapy (see section 5.1).*"

CHMP considered that this proposal did not reflect the studied population. CHMP noted that the majority (50.9%) of patients used only 2 ISTs. In order to substantiate whether the use of immunomodulatory therapy (including the number of therapies received) has an impact on the efficacy of ravulizumab and defines the target population who should receive ravulizumab in clinical practice additional analyses were provided. With respect to prior use of IST, this does not appear to have a relevant impact on the effect of ravulizumab. And when it is observed it seems to be likely driven by the low number of subjects.

With respect to the available evidence in other subsets of the population that are covered by the broad indication proposed, e.g. MFGA class IV and V subjects further clarifications have been presented.

a. there were only 9 patients with a MGFA Class IV, included in the study. The mean treatment difference in MG-ADL total score was -7.2 [3.26] (95% CI: -14.9, 0.4; p = 0.0593). The mean treatment difference in QMG total score was -4.4 [2.35]; (95% CI: -9.4, 0.7; p =0.0836). The results do not suggest that ravulizumab does not have an effect in these patients.

b. patients with a MGFA Class V were excluded from the study. Available postmarketing data on the use of eculizumab nin Japan showing a similar response in these patients to that achieved by less severe patients. Give the similarities with ravulizumab in principle there are not reasons for restricting the use of ravulizumab in this subset. However, the lack of Class V gMG patients treated with ravulizumab has been reflected in the SmPC.

Further justifications were provided to address the concerns raised regarding the wording of the indication and the appropriateness of adopting an indication similar to that approved for eculizumab. It was highlighted that there are several differences between both clinical developments. The provided justification aims at addressing various aspects:

a) There are differences in the selection criteria of pivotal study conducted with eculizumab (Study ECU-MG-301) and that conducted with ravulizumab (Study ALXN1210-MG-306). Whereas the patients enrolled in the eculizumab study were required to have failed to a previous treatment with

≥2 IST or ≥1 IST + PE/IVIg, patients included in the ravulizumab study had no requirement for treatment failure. In this case the study allowed patients with/without concomitant treatment.

b) The comparison of the populations enrolled in eculizumab and ravulizumab studies shows that in general the eculizumab population had more severe disease at entry than the ravulizumab population.

c) Patients in the eculizumab study had received more lines of treatment than patients included in the ravulizumab study.

    - In the eculizumab study 46.4% of patients had received ≥2 ISTs; 31.2% ≥3 ISTs and 20.8% ≥4 ISTs; 79.2% had received IVIg and 48.0% PP/PE.
    - In the ravulizumab study 19.4% of patients had received only 1 IST; 50.9% only 2 ISTs, 43.4% had received IVIg and 19.4% PP/PE. A total of 6 patients had no received prior therapy at entry.

d) The concomitant treatment at entry in patients receiving ravulizumab was as follows: 10.3% of patients were receiving no concomitant treatment with ISTs, 42.3% were using only 1 IST, and 47.4% were using 2 or more ISTs. These numbers have not been provided for eculizumab patients.

In general, patients included in the eculizumab study seems to correspond to a more severe, more heavily treated patients, in accordance with the approved indication in a refractory population, while the patient population included in the ravulizumab study would justify granting a broader indication.

As such, the wording of the approved indication for ravulizumab was amended as follows:

*"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."*

### 2.4.4. Conclusions on the clinical efficacy

The effect of ravulizumab over placebo on the control of symptoms assessed by the patient (MG-ADL score, primary endpoint) and by the physician (QMG score; secondary endpoint) has been demonstrated. A consistent treatment effect has been shown based on available efficacy data that, even if of modest magnitude in the short-term, it can be considered a sufficiently robust demonstration of the clinical benefit of ravulizumab when added to standard therapy in patients with gMG. The findings from the (updated) Extension open label period further support the maintenance of the effect in this population. The final results of the study will have to be submitted once available.

## *2.5. Clinical safety*

### *Introduction*

The overall safety evaluation is based on the following data from Study ALXN1210 MG 306:

- Randomized Controlled Period – data for the randomized, double-blind, placebo- controlled 26-week treatment period.

- Ravulizumab Treatment Period – data through the 52 week data cut-off date (11 May 2021) were included for patients who had reached Week 52 or were expected to reach Week 52 by the time of

the data cutoff date (ie, including patients who had withdrawn from the study prior to Week 52). Results for the Ravulizumab Treatment Period include data from:

- Patients treated with ravulizumab during the Randomized-Controlled Period regardless of whether the patients continued to receive treatment with ravulizumab during the Open-Label Extension Period (referred to as the RAV/RAV group)
- Patients treated with placebo during the Randomized-Controlled Period and who switched to ravulizumab in the Open-Label Extension Period (referred to as the PBO/RAV group)

All safety analyses for the Randomized-Controlled Period are presented for the *Safety Set* which consisted of all patients who received at least 1 dose of study drug (ravulizumab or placebo).

All safety analyses for the Ravulizumab Treated Period are presented for the Ravulizumab Treated Set which consisted of all patients who received at least 1 dose of ravulizumab either in the Randomized-Controlled Period or the Open-Label Extension Period.

Subgroup analyses were based on geographic region, sex, race, age at first study drug infusion, immunosuppressive therapy (IST) use at baseline, years from diagnosis to informed consent, baseline MGFA clinical classification, and baseline body weight categories.

## *Patient exposure*

In total, 175 patients were randomized and treated (placebo: n = 89; ravulizumab: n = 86). Thirteen patients withdrew from the study prior to completing the Randomized-Controlled Period, including 2 patients who discontinued study drug due to AEs and 2 patients who died (cerebral hemorrhage and COVID-19 pneumonia).

As of the clinical database cutoff date, 75 of the 79 patients in the Open-Label Extension Set (ie, all patients who received at least 1 dose of ravulizumab starting from Week 26 and who have completed Week 52 study visit or who would have completed Week 52 by the data cutoff date but withdrew from the study) had completed the Week 52 Visit. Four of the 79 patients in the Open-Label Extension Set had withdrawn from the study during the Open-Label Extension Period (2 due to patient decision and 2 deaths due to COVID-19). A total of 75 patients were ongoing in the Open-Label Extension Period as of the 52-week data cutoff date: 35 patients who received ravulizumab during both the Randomized-Controlled Period and the Open-Label Extension Period, and 40 patients who received placebo during the Randomized-Controlled Period and switched to ravulizumab in the Open-Label Extension Period.

**Table 31: Patient Disposition During the Randomized-Controlled Period (All Randomized Patients)**

| | **Placebo (N=89)** | | **Ravulizumab (N=86)** | | **Total (N=175)** | |
|---|---|---|---|---|---|---|
| | **Overall** | **COVID-19 Related** | **Overall** | **COVID-19 Related** | **Overall** | **COVID-19 Related** |
| Randomized[a], n (%) | 89 (100) | | 86 (100) | | 175 (100) | |
| Treated, n (%) | 89 (100) | | 86 (100) | | 175 (100) | |
| Completed Randomized-Controlled Period (Week 26), n (%) | 83 (93.3) | | 79 (91.9) | | 162 (92.6) | |
| Did not Complete Randomized-Controlled Period (Week 26), n (%) | 6 (6.7) | 0 | 7 (8.1) | 3 (3.5) | 13 (7.4) | 3 (1.7) |
| Death | 0 | 0 | 2 (2.3) | 1 (1.2) | 2 (1.1) | 1 (0.6) |
| Withdrawal by patient | 1 (1.1) | 0 | 2 (2.3) | 0 | 3 (1.7) | 0 |
| Noncompliance with study drug | 0 | 0 | 1 (1.2) | 1 (1.2) | 1 (0.6) | 1 (0.6) |
| Physician decision | 2 (2.2) | 0 | 1 (1.2) | 1 (1.2) | 3 (1.7) | 1 (0.6) |
| Protocol violation | 0 | 0 | 1 (1.2) | 0 | 1 (0.6) | 0 |
| Adverse event | 2 (2.2) | 0 | 0 | 0 | 2 (1.1) | 0 |

| | Placebo (N=89) | | Ravulizumab (N=86) | | Total (N=175) | |
|---|---|---|---|---|---|---|
| | Overall | COVID-19 Related | Overall | COVID-19 Related | Overall | COVID-19 Related |
| Other[b] | 1 (1.1) | 0 | 0 | 0 | 1 (0.6) | 0 |

Note: Reasons for study withdrawal due to COVID-19 are also presented in the overall column.

[a] Two additional patients were randomized in error: 1 patient was randomized but could not be dosed due to a water leak in the laminar hood while preparing study drug; patient was ultimately screen failed. Additionally, 1 patient was randomized and screen failed due to pyridostigmine not being withheld 10 hours prior to Screening assessments; this patient was subsequently re-screened and re-randomized (patient was counted in the "Randomized" row).

[b] Other reason = Sponsor's request, measuring complement-related protein that could have led to potential unblinding (ie, the assessment would be biased)

Abbreviations: COVID-19 = coronavirus disease 19

Overall, 50.9% of patients in the Safety Analysis Set were female; 73.1% were White, and the mean age was 55.6 years at the time of first infusion. The majority of patients (69.1%) were 18 to 65 years of age at the time of first infusion, and approximately half of the patients (53.7%) were in the weight category ≥ 60 kg to < 100 kg at baseline.

Overall, 82 (47%) patients (placebo: 39 [44%]; ravulizumab: 43 [50%]) had hospitalizations within 2 years prior to Screening; mean number of hospitalizations was 2.3 for both treatment groups. A majority of these patients had hospitalizations related to MG (placebo: 32/39 patients; ravulizumab: 32/43 patients); mean number of MG-related hospitalizations was 2.0 for both treatment groups.

## *Adverse events*

The safety profile for ravulizumab was similar to that of placebo in adult patients with gMG during the 26-week Randomized-Controlled Period (Table32).

**Table 32: Overview of All Treatment-Emergent Adverse Events During the Randomized-Controlled Period (ALXN1210-MG-306 Safety Set)**

| | Placebo (N = 89) | Ravulizumab (N = 86) |
|---|---|---|
| | n (%) | n (%) |
| Any AE | 77 (86.5) | 78 (90.7) |
| Any SAE | 14 (15.7) | 20 (23.3) |
| Death | 0 | 2 (2.3) |
| AE leading to discontinuation of study drug | 3 (3.4) | 2 (2.3) |
| SAE leading to discontinuation of study drug | 1 (1.1) | 2 (2.3) |
| AE by relationship to study drug | | |
| Related | 30 (33.7) | 29 (33.7) |
| Not related | 72 (80.9) | 76 (88.4) |
| AE by severity[a] | | |
| Grade 1 | 66 (74.2) | 65 (75.6) |
| Grade 2 | 30 (33.7) | 39 (45.3) |
| Grade 3 | 14 (15.7) | 19 (22.1) |
| Grade 4 | 1 (1.1) | 4[b] (4.7) |
| Grade 5 | 0 | 2 (2.3) |
| SAE by relationship to study drug | | |
| Related | 4 (4.5) | 2 (2.3) |
| Not related | 11 (12.4) | 18 (20.9) |

Note: Patients were counted once in each severity or relationship category in case of multiple events. Treatment-emergent AEs were AEs with a start date on or after first dose date in the study. AEs were coded using MedDRA Version 24.0.

[a] Severity of AEs was graded using CTCAE Version 5.0. Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = fatal.

[b] Two of the 4 patients had Grade 4 SAEs that subsequently resulted in death (Grade 5) (ie, events were counted in both severity categories).

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event

During the Ravulizumab Treatment Period, 86.6% of patients experienced at least 1 AE (Table 33).

As of the data cut-off date, 4 patients died during the study and no meningococcal infections were observed.

**Table 33: Overview of All Treatment-emergent Adverse Events Since First Dose of Ravulizumab as of Data Cutoff Date (ALXN1210-MG-306 Ravulizumab Treated Set)**

| | Total | | |
|---|---|---|---|
| | 0 to 6 mo (N = 127) n (%) | > 6 to 12 mo (N = 97) n (%) | 0 to cutoff (N = 127) n (%) |
| Any AE | 109 (85.8) | 34 (35.1) | 110 (86.6) |
| Any SAE | 25 (19.7) | 5 (5.2) | 27 (21.3) |
| Death | 2 (1.6) | 2 (2.1) | 4 (3.1) |
| AE leading to discontinuation of study drug | 2 (1.6) | 0 | 2 (1.6) |
| SAE leading to discontinuation of study drug | 2 (1.6) | 0 | 2 (1.6) |
| AE by relationship to study drug | | | |
| Related | 40 (31.5) | 10 (10.3) | 43 (33.9) |
| Not related | 104 (81.9) | 31 (32.0) | 107 (84.3) |
| AE by severity[a] | | | |
| Grade 1 | 89 (70.1) | 30 (30.9) | 90 (70.9) |
| Grade 2 | 47 (37.0) | 12 (12.4) | 54 (42.5) |
| Grade 3 | 24 (18.9) | 3 (3.1) | 27 (21.3) |
| Grade 4 | 5 (3.9) | 0 | 5[b] (3.9) |
| Grade 5 | 2 (1.6) | 2 (2.1) | 4 (3.1) |
| SAE by relationship to study drug | | | |
| Related | 3 (2.4) | 0 | 3 (2.4) |
| Not related | 22 (17.3) | 5 (5.2) | 24 (18.9) |

Note: The Ravulizumab Treated Set consisted of all patients who received at least 1 dose of ravulizumab either in the Randomized-Controlled Period or the Open-Label Extension Period. Per scope, only data during Randomized-Controlled Period were included for patients not expected to have Week 52 at data cutoff. This would apply to both ravulizumab and placebo patients. Patients were counted once in each severity or relationship category in case of multiple events. At the time of the data cutoff date, data for only 13 patients receiving ravulizumab treatment > 12 months was available; 2 of the 13 patients reported AEs during this period. AEs were coded using MedDRA Version 24.0.

[a] Severity of AEs was graded using CTCAE Version 5.0. Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = fatal.

[b] Two of the 5 patients had Grade 4 SAEs that subsequently resulted in death (Grade 5) (ie, events were counted in both severity categories).

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; mo = months; SAE = serious adverse event

**As of the 60-week CSR cut-off date**, the mean duration of ravulizumab treatment is 306.1 days, and the maximum is 442.0 days (Table 34). Total exposure to ravulizumab was 141.6 patient-years, compared to 81.5 patient-years in the initial CSR.

**Table 34: Treatment Administration During the Ravulizumab Treatment Period Through the Data Cut-off Date (Ravulizumab Treated Set)**

| Variable | PBO/RAV (N = 83) | RAV/RAV (N = 86) | Total (N = 169) |
|---|---|---|---|
| Study duration from informed consent[a] (days) | | | |
| Mean (SD) | 430.7 (31.59) | 406.7 (85.13) | 418.4 (65.56) |
| Median | 442.0 | 441.0 | 442.0 |
| Min, max | 269.0, 461.0 | 40.0, 466.0 | 40.0, 466.0 |
| Ravulizumab treatment duration[b] (days) | | | |
| Mean (SD) | 225.6 (31.43) | 383.8 (85.20) | 306.1 (102.18) |
| Median | 239.0 | 421.0 | 246.0 |
| Min, max | 63.0, 258.0 | 14.0, 442.0 | 14.0, 442.0 |
| Ravulizumab treatment duration category, n (%) | | | |
| > 0 to 6 months | 3 (3.6) | 6 (7.0) | 9 (5.3) |
| > 6 to 12 months | 80 (96.4) | 5 (5.8) | 85 (50.3) |
| > 12 to 18 months | 0 (0.0) | 75 (87.2) | 75 (44.4) |
| > 18 to 24 months | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| > 24 months | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Patient-years of exposure to ravulizumab | 51.3 | 90.4 | 141.6 |
| Number of ravulizumab infusions per patient | | | |
| Mean (SD) | 5.7 (0.86) | 9.2 (2.34) | 7.4 (2.50) |
| Median | 6.0 | 10.0 | 6.0 |
| Min, max | 2.0, 8.0 | 1.0, 15.0 | 1.0, 15.0 |
| Total infusions | 469 | 788 | 1257 |

Note: The Ravulizumab Treated Set consists of all patients who received at least 1 dose of ravulizumab either in the Randomized-Controlled Period or the Open-Label Extension Period. Data up to Week 60 at data cutoff date are included.
a Study duration = data cutoff date/discontinuation – date of informed consent + 1.
b Ravulizumab treatment duration = data cutoff date/discontinuation – first ravulizumab infusion date + 1.
Abbreviations: max = maximum; Min = minimum ; PBO = placebo; RAV = ravulizumab; SD = standard deviation

**Common Adverse Events**

During the Randomized-Controlled Period, the most frequently reported AEs (≥ 10% of all patients) were headache (placebo: 25.8%; ravulizumab: 18.6%), diarrhoea (placebo: 12.4%; ravulizumab: 15.1%), and nausea (placebo: 10.1%; ravulizumab: 10.5%) (Table 35).

**Table 35: Treatment-emergent Adverse Events Experienced by 5% or More of Patients in Any Treatment Group During the Randomized-Controlled Period (ALXN1210-MG-306 Safety Set)**

| System Organ Class<br>Preferred Term | Placebo (N = 89)<br>n (%) | Ravulizumab (N = 86)<br>n (%) | Total (N = 175)<br>n (%) |
|---|---|---|---|
| Any AE | 77 (86.5) | 78 (90.7) | 155 (88.6) |
| Infections and infestations | 28 (31.5) | 38 (44.2) | 66 (37.7) |
| COVID-19 | 3 (3.4) | 5 (5.8) | 8 (4.6) |
| Urinary tract infection | 4 (4.5) | 5 (5.8) | 9 (5.1) |
| Nasopharyngitis | 5 (5.6) | 3 (3.5) | 8 (4.6) |
| Nervous system disorders | 32 (36.0) | 30 (34.9) | 62 (35.4) |
| Headache | 23 (25.8) | 16 (18.6) | 39 (22.3) |
| Dizziness | 3 (3.4) | 8 (9.3) | 11 (6.3) |
| Gastrointestinal disorders | 29 (32.6) | 29 (33.7) | 58 (33.1) |
| Diarrhoea | 11 (12.4) | 13 (15.1) | 24 (13.7) |
| Nausea | 9 (10.1) | 9 (10.5) | 18 (10.3) |
| Abdominal pain | 0 | 5 (5.8) | 5 (2.9) |
| Musculoskeletal and connective tissue disorders | 23 (25.8) | 23 (26.7) | 46 (26.3) |
| Back pain | 5 (5.6) | 7 (8.1) | 12 (6.9) |
| Arthralgia | 7 (7.9) | 6 (7.0) | 13 (7.4) |
| General disorders and administration site conditions | 21 (23.6) | 22 (25.6) | 43 (24.6) |
| Fatigue | 6 (6.7) | 6 (7.0) | 12 (6.9) |
| Pyrexia | 5 (5.6) | 1 (1.2) | 6 (3.4) |
| Injury, poisoning and procedural complications | 17 (19.1) | 6 (7.0) | 23 (13.1) |
| Infusion-related reaction | 5 (5.6) | 0 | 5 (2.9) |

Note: In summarizing n (%), if a patient had multiple events for a particular SOC or Preferred Term, he/she was counted only once for that SOC or Preferred Term. Results were sorted by Ravulizumab column in descending order of SOC percentage and then Preferred Term within SOC. AEs were coded using MedDRA 24.0.
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class

As of the data cut-off date, the most frequently reported AEs (≥ 10% of total patients) in the Ravulizumab Treated Set, were headache (18.1%), diarrhoea (12.6%), and nausea (10.2%) (Table 36). Of the patients who experienced headaches, most of the AEs of headache (24 of 30 events) occurred during the first 6 months of treatment.

**Table 36: Treatment-emergent Adverse Events in by 5% or More of Patients During the Ravulizumab Treatment Period Through the Data Cutoff Date (ALXN1210-MG-306 Ravulizumab Treated Set)**

| System Organ Class<br>Preferred term | Total | | |
|---|---|---|---|
| | 0 to 6 mo<br>(N = 127)<br>n (%) | > 6 to 12 mo<br>(N = 97)<br>n (%) | 0 to cutoff<br>(N = 127)<br>n (%) |
| Any AE | 109 (85.8) | 34 (35.1) | 110 (86.6) |
| Infections and infestations | 51 (40.2) | 13 (13.4) | 57 (44.9) |
| Urinary tract infection | 7 (5.5) | 1 (1.0) | 9 (7.1) |
| Upper respiratory tract infection | 7 (5.5) | 1 (1.0) | 8 (6.3) |
| COVID-19 | 6 (4.7) | 2 (2.1) | 7 (5.5) |
| Nervous system disorders | 38 (29.9) | 8 (8.2) | 42 (33.1) |
| Headache | 21 (16.5) | 3 (3.1) | 23 (18.1) |
| Dizziness | 10 (7.9) | 3 (3.1) | 11 (8.7) |
| Gastrointestinal disorders | 38 (29.9) | 6 (6.2) | 41 (32.3) |
| Diarrhoea | 14 (11.0) | 2 (2.1) | 16 (12.6) |
| Nausea | 12 (9.4) | 3 (3.1) | 13 (10.2) |
| Abdominal pain | 7 (5.5) | 1 (1.0) | 8 (6.3) |
| Musculoskeletal and connective tissue disorders | 27 (21.3) | 8 (8.2) | 32 (25.2) |
| Arthralgia | 8 (6.3) | 1 (1.0) | 9 (7.1) |
| Back pain | 7 (5.5) | 1 (1.0) | 8 (6.3) |
| General disorders and administration site conditions | 26 (20.5) | 10 (10.3) | 29 (22.8) |
| Fatigue | 6 (4.7) | 3 (3.1) | 8 (6.3) |

Note: The Ravulizumab Treated Set consisted of all patients who received at least 1 dose of ravulizumab either in the Randomized-Controlled Period or the Open-Label Extension Period. Per scope, only data during the Randomized-Controlled Period were included for patients not expected to have Week 52 at data cutoff. This applied to both RAV/RAV and PBO/RAV patients. In summarizing n (%), if a patient had multiple events for a particular SOC or Preferred Term, the patient was counted only once for that SOC or Preferred Term. At the time of the data cutoff date, data for only 13 patients receiving ravulizumab treatment > 12 months were available; 2 of the 13 patients reported AEs during this period (ALXN1210-MG-306 CSR Table 14.3.3.1.1.4). AEs were coded using MedDRA Version 24.0.
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; mo = months; SOC = system organ class

**Adverse Events Through Week 60**

During the Ravulizumab Treatment Period, 88.8% of patients experienced at least 1 adverse event (AE; 881 events) (Table 37).

At least 1 treatment-emergent serious adverse event (SAE) was experienced by 41 (24.3%) patients (75 events). Seven (4.1%) patients (10 events) had SAEs related to coronavirus disease 2019 (COVID-19) or suspected COVID 19. Five (3%) patients experienced an SAE assessed as related to investigational product.

A total of 3 patients in the RAV/RAV group had SAEs which led to discontinuation of study drug. SAEs of infected skin ulcer and COVID-19 pneumonia with fatal outcome occurred in 1 patient each during the Randomized Controlled Period; and 1 SAE of myasthenia gravis occurred in 1 patient during the Open-Label Extension Period.

Of the 881 AEs in the Ravulizumab Treatment Period, most AEs were Grade 1 or Grade 2 in severity.

A total of 30 (17.8%) patients in the Ravulizumab Treated Set experienced AEs that had a maximum severity of Grade 3. All the Grade 3 AEs occurred in 1 patient each with the exception of pyrexia, pneumonia, syncope, dyspnea, urticaria, and hypertension (2 patients each) and myasthenia gravis (4 patients).

Seven (4.1%) patients experienced AEs that had a maximum severity of Grade 4 which included: headache, hypotension, vein rupture, appendicitis, arthritis bacterial, COVID-19 pneumonia, and suspected COVID-19.

**Table 37: Overview of Treatment-Emergent Adverse Events During the Ravulizumab Treatment Period Through Week 60 as of the Data Cutoff Date (Ravulizumab Treated Set)**

| | Total Treatment Duration with Ravulizumab | | | |
|---|---|---|---|---|
| | 0 to 6 months (N = 169) n (%) | > 6 to 12 months (N = 160) n (%) | > 12 to 18 months (N = 75) n (%) | 0 to Cutoff (N = 169) n (%) |
| Any AE | 143 (84.6) | 90 (56.3) | 23 (30.7) | 150 (88.8) |
| Any SAE | 30 (17.8) | 18 (11.3) | 2 (2.7) | 41 (24.3) |
| Death | 2 (1.2) | 2 (1.3) | 0 | 4 (2.4) |
| AE leading to discontinuation of study drug | 2 (1.2) | 1 (0.6) | 0 | 3 (1.8) |
| SAE leading to discontinuation of study drug | 2 (1.2) | 1 (0.6) | 0 | 3 (1.8) |
| AE by relationship to study drug | | | | |
| Related | 50 (29.6) | 19 (11.9) | 7 (9.3) | 58 (34.3) |
| Not related | 138 (81.7) | 84 (52.5) | 20 (26.7) | 148 (87.6) |
| AE by severity[a] | | | | |
| Grade 1 | 116 (68.6) | 72 (45.0) | 15 (20.0) | 127 (75.1) |
| Grade 2 | 63 (37.3) | 39 (24.4) | 10 (13.3) | 82 (48.5) |
| Grade 3 | 28 (16.6) | 13 (8.1) | 2 (2.7) | 39 (23.1) |
| Grade 4 | 7 (4.1) | 2 (1.3) | 0 | 9 (5.3) |
| Grade 5 | 2 (1.2) | 2 (1.3) | 0 | 4 (2.4) |
| SAE by relationship to study drug | | | | |
| Related | 4 (2.4) | 1 (0.6) | 0 | 5 (3.0) |
| Not related | 26 (15.4) | 18 (11.3) | 2 (2.7) | 38 (22.5) |

Note: The Ravulizumab Treated Set consisted of all patients who received at least 1 dose of ravulizumab either in the Randomized-Controlled Period or the Open-Label Extension Period. Data up to Week 60 at data cut-off date are included. Patients were counted once in each severity or relationship category in case of multiple events. AEs were coded using MedDRA Version 24.1.
a Severity of AEs was graded using CTCAE Version 5.0. Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = fatal.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event

### Adverse Events of Special Interest

As of the 52-week data cut-off date, no meningococcal infections were reported during the study.

### Infusion Reactions

Local (infusion site or injection site reactions), systemic (infusion-associated/infusion-related reactions), and immune-mediated reactions were evaluated during the Randomized-Controlled Period.

**Table 38: Definitions for Infusion Reactions Local Administration Reaction**

| | Systemic Reaction | Immune-mediated Reactions |
|---|---|---|

| | | |
|---|---|---|
| Infusion site/ injection site reactions | Infusion-associated/ Infusion-related reactions | Hypersensitivity |
| AEs localized to the site of study drug administration | Systemic AEs occurring during or within 24 hours of the start of infusion (eg, fever and/or shaking chills, flushing and/or itching, etc.) | AEs with Preferred Terms in the narrow SMQ of Anaphylactic reaction and the narrow SMQ of Hypersensitivity |

Abbreviations: AE = adverse event; SMQ = Standardised MedDRA (Medical Dictionary for Regulatory Activities) Query

The percentage of patients who reported infusion reactions during the Randomized-Controlled Period was similar between the treatment groups (Table 39). The most common infusion reaction was headache (placebo: 15.7%; ravulizumab: 11.6%). All events of infusion-related reactions occurred in the placebo group.

**Table 39: Infusion Reactions During the Randomized-Controlled Period (Safety Set)**

| **System Organ Class**<br>**Preferred Term** | **Placebo (N=89)** | **Ravulizumab (N=86)** | **Total (N=175)** |
|---|---|---|---|
| | **n (%)** | **n (%)** | **n (%)** |
| Any infusion reaction | 28 (31.5) | 28 (32.6) | 56 (32.0) |
| Nervous system disorders | 15 (16.9) | 13 (15.1) | 28 (16.0) |
| Headache | 14 (15.7) | 10 (11.6) | 24 (13.7) |
| Dizziness | 3 (3.4) | 4 (4.7) | 7 (4.0) |
| Gastrointestinal disorders | 9 (10.1) | 11 (12.8) | 20 (11.4) |
| Nausea | 5 (5.6) | 7 (8.1) | 12 (6.9) |
| Diarrhoea | 3 (3.4) | 5 (5.8) | 8 (4.6) |
| Abdominal pain | 0 | 2 (2.3) | 2 (1.1) |
| Vomiting | 1 (1.1) | 1 (1.2) | 2 (1.1) |
| Abdominal distension | 1 (1.1) | 0 | 1 (0.6) |
| General disorders and administration site conditions | 6 (6.7) | 10 (11.6) | 16 (9.1) |
| Fatigue | 3 (3.4) | 3 (3.5) | 6 (3.4) |
| Asthenia | 0 | 1 (1.2) | 1 (0.6) |
| Chills | 0 | 1 (1.2) | 1 (0.6) |
| Infusion site extravasation | 0 | 1 (1.2) | 1 (0.6) |
| Infusion site haematoma | 0 | 1 (1.2) | 1 (0.6) |
| Infusion site pain | 0 | 1 (1.2) | 1 (0.6) |
| Injection site reaction | 0 | 1 (1.2) | 1 (0.6) |
| Vaccination site irritation | 0 | 1 (1.2) | 1 (0.6) |
| Vaccination site reaction | 0 | 1 (1.2) | 1 (0.6) |
| Catheter site erythema | 1 (1.1) | 0 | 1 (0.6) |
| Injection site bruising | 1 (1.1) | 0 | 1 (0.6) |
| Pyrexia | 1 (1.1) | 0 | 1 (0.6) |
| Skin and subcutaneous tissue disorders | 3 (3.4) | 3 (3.5) | 6 (3.4) |
| Rash | 2 (2.2) | 2 (2.3) | 4 (2.3) |
| Pruritus | 0 | 1 (1.2) | 1 (0.6) |
| Eczema | 1 (1.1) | 0 | 1 (0.6) |
| Urticaria | 1 (1.1) | 0 | 1 (0.6) |
| Respiratory, thoracic and mediastinal disorders | 1 (1.1) | 2 (2.3) | 3 (1.7) |
| Dyspnoea | 0 | 2 (2.3) | 2 (1.1) |
| Rhinitis allergic | 1 (1.1) | 0 | 1 (0.6) |
| Eye disorders | 1 (1.1) | 1 (1.2) | 2 (1.1) |
| Swelling of eyelid | 0 | 1 (1.2) | 1 (0.6) |
| Eye swelling | 1 (1.1) | 0 | 1 (0.6) |
| Immune system disorders | 0 | 1 (1.2) | 1 (0.6) |
| Drug hypersensitivity | 0 | 1 (1.2) | 1 (0.6) |
| Musculoskeletal and connective tissue disorders | 0 | 1 (1.2) | 1 (0.6) |
| Arthralgia | 0 | 1 (1.2) | 1 (0.6) |
| Vascular disorders | 2 (2.2) | 1 (1.2) | 3 (1.7) |
| Hypertension | 2 (2.2) | 1 (1.2) | 3 (1.7) |
| Injury, poisoning and procedural complications | 6 (6.7) | 0 | 6 (3.4) |
| Infusion related reaction | 5 (5.6) | 0 | 5 (2.9) |
| Injection related reaction | 1 (1.1) | 0 | 1 (0.6) |

**Table 39: Infusion Reactions During the Randomized-Controlled Period (Safety Set)**

| System Organ Class<br>Preferred Term | Placebo<br>(N=89) | Ravulizumab<br>(N=86) | Total<br>(N=175) |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Psychiatric disorders | 1 (1.1) | 0 | 1 (0.6) |
| Anxiety | 1 (1.1) | 0 | 1 (0.6) |

Notes: In summarizing n (%), if a patient had multiple events for a particular SOC or preferred term, he/she was counted only once for that SOC or preferred term. Treatment emergent AEs are AEs with a start date on or after first dose date in the study. Results were sorted by Ravulizumab column in descending order of SOC percentage and then PT within SOC. AEs were coded using MedDRA 24.0.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class

Only 1 patient (placebo group) had an infusion reaction that was a SAE (infusion-related reaction) during the Randomized-Controlled Period. Two patients in the placebo group had infusion interruptions and withdrew from the study due to infusion reactions. One patient in the ravulizumab group had an infusion interruption due to infusion site extravasation on Day 69.

Infusion Reactions Through Week 60

Local (infusion site or injection site reactions), systemic (infusion-associated/infusion-related reactions), and immune-mediated reactions as defined in Table 40 were evaluated during the Randomized-Controlled Period.

**Table 40: Definitions for Infusion Reactions**

| Local Administration Reaction | Systemic Reaction | Immune-mediated Reactions |
|---|---|---|
| Infusion site/ injection site reactions | Infusion-associated/ Infusion-related reactions | Hypersensitivity |
| AEs localized to the site of study drug administration | Systemic AEs occurring during or within 24 hours of the start of infusion (eg, fever and/or shaking chills, flushing and/or itching, etc.) | AEs with Preferred Terms in the narrow SMQ of Anaphylactic reaction and the narrow SMQ of Hypersensitivity |

Abbreviations: AE = adverse event; SMQ = Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query

A total of 59 (34.9%) patients reported infusion reactions during the Ravulizumab Treatment Period. The most common infusion reactions were headache (11.2%) and nausea (6.5%). A total of 9 infusions in 8 patients had interruptions due to AEs. In 7 of the 8 patients, the infusion was subsequently re-started and completed.

## *Serious adverse event/deaths/other significant events*

Other Serious Adverse Events During the Randomized-Controlled Period

Overall, 34 (19.4%) patients in the Safety Set experienced 1 or more SAEs (51 events) during the Randomized-Controlled Period; 14 (15.7%) patients in the placebo group and 20 (23.3%) patients in the ravulizumab group (Table ).

Four (4.5%) patients in the placebo group and 7 (8.1%) patients in the ravulizumab group had SAEs in the SOC of Infections and infestations: all SAEs of infections were observed in 1 patient each, with the exception of COVID-19 pneumonia (ravulizumab: n = 2) and cellulitis (placebo: n = 2). A higher percentage of patients in the ravulizumab group reported AEs in the SOCs of Infection and infestations and Respiratory, thoracic, and mediastinal disorders. The AEs reported in the SOC of Respiratory,

thoracic, and mediastinal disorders were consistent with symptoms of the underlying disease and/or comorbid diseases.

Two patients in the ravulizumab group had SAEs of transient ischemic attack; both events were assessed as not related to study drug by the Investigator: 1 patient had a history of supraventricular tachycardia, hypertension, and coronary artery disease and 1 patient had a history of hypertension and dyslipidaemia.

Three patients had SAEs that resulted in discontinuation of study drug.

Three patients had SAEs that resulted in interruption of study treatment: 2 patients in the placebo group (herpes zoster and cellulitis) and 1 patient in the ravulizumab group (bacterial arthritis).

Six patients had SAEs that were assessed to be related to study drug by the Investigator; 4 patients in the placebo group (cellulitis: n = 2; herpes zoster: n = 1; and infusion-related reaction: n = 1) and 2 patients in the ravulizumab group (dysphagia: n = 1; tendonitis: n = 1).

One patient in the ravulizumab group had an SAE of suicide attempt; the patient was hospitalized on Day 122 and discharged on Day 132. The patient had a prior history of depression and suicide attempt and this event was assessed as not related to study drug by the Investigator.

**Table 41: Treatment-emergent Serious Adverse Events During the Randomized-Controlled Period by System Organ Class and Preferred Term (ALXN1210-MG-306 Safety Set)**

| System Organ Class<br>Preferred Term | Placebo<br>(N = 89)<br>n (%) | Ravulizumab<br>(N = 86)<br>n (%) | Total<br>(N = 175)<br>n (%) |
|---|---|---|---|
| Any SAE | 14 (15.7) | 20 (23.3) | 34 (19.4) |
| Infections and infestations | 4 (4.5) | 7 (8.1) | 11 (6.3) |
| COVID-19 pneumonia | 0 | 2 (2.3) | 2 (1.1) |
| Arthritis bacterial | 0 | 1 (1.2) | 1 (0.6) |
| Diverticulitis | 0 | 1 (1.2) | 1 (0.6) |
| Gangrene | 0 | 1 (1.2) | 1 (0.6) |
| Gastroenteritis viral | 0 | 1 (1.2) | 1 (0.6) |
| Herpes zoster | 1 (1.1) | 1 (1.2) | 2 (1.1) |
| Infected skin ulcer | 0 | 1 (1.2) | 1 (0.6) |
| Pneumonia respiratory syncytial viral | 0 | 1 (1.2) | 1 (0.6) |
| Staphylococcal sepsis | 0 | 1 (1.2) | 1 (0.6) |
| COVID-19 | 1 (1.1) | 0 | 1 (0.6) |
| Cellulitis | 2 (2.2) | 0 | 2 (1.1) |
| Nervous system disorders | 4 (4.5) | 5 (5.8) | 9 (5.1) |
| Transient ischaemic attack | 0 | 2 (2.3) | 2 (1.1) |
| Cerebral haemorrhage | 0 | 1 (1.2) | 1 (0.6) |
| Myasthenia gravis crisis[a] | 0 | 1 (1.2) | 1 (0.6) |
| Syncope | 0 | 1 (1.2) | 1 (0.6) |
| Facial paresis | 1 (1.1) | 0 | 1 (0.6) |
| Myasthenia gravis | 3 (3.4) | 0 | 3 (1.7) |
| Trigeminal neuralgia | 1 (1.1) | 0 | 1 (0.6) |
| Musculoskeletal and connective tissue disorders | 1 (1.1) | 3 (3.5) | 4 (2.3) |
| Intervertebral disc protrusion | 0 | 1 (1.2) | 1 (0.6) |
| Nodal osteoarthritis | 0 | 1 (1.2) | 1 (0.6) |
| Tendonitis | 0 | 1 (1.2) | 1 (0.6) |
| Spinal stenosis | 1 (1.1) | 0 | 1 (0.6) |
| Respiratory, thoracic, and mediastinal disorders | 0 | 3 (3.5) | 3 (1.7) |
| Dyspnoea | 0 | 1 (1.2) | 1 (0.6) |
| Dyspnoea exertional | 0 | 1 (1.2) | 1 (0.6) |
| Lung infiltration | 0 | 1 (1.2) | 1 (0.6) |
| Gastrointestinal disorders | 1 (1.1) | 2 (2.3) | 3 (1.7) |
| Dysphagia | 0 | 1 (1.2) | 1 (0.6) |
| Nausea | 0 | 1 (1.2) | 1 (0.6) |
| Enteritis | 1 (1.1) | 0 | 1 (0.6) |
| General disorders and administration site conditions | 0 | 2 (2.3) | 2 (1.1) |
| Asthenia | 0 | 1 (1.2) | 1 (0.6) |
| General physical health deterioration | 0 | 1 (1.2) | 1 (0.6) |
| Non-cardiac chest pain | 0 | 1 (1.2) | 1 (0.6) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0 | 2 (2.3) | 2 (1.1) |
| Squamous cell carcinoma of skin | 0 | 1 (1.2) | 1 (0.6) |
| Ureteral neoplasm | 0 | 1 (1.2) | 1 (0.6) |
| Cardiac disorders | 0 | 1 (1.2) | 1 (0.6) |
| Congestive cardiomyopathy | 0 | 1 (1.2) | 1 (0.6) |
| Eye disorders | 0 | 1 (1.2) | 1 (0.6) |
| Visual impairment | 0 | 1 (1.2) | 1 (0.6) |
| Injury, poisoning and procedural complications | 1 (1.1) | 1 (1.2) | 2 (1.1) |
| Multiple fractures | 0 | 1 (1.2) | 1 (0.6) |
| Infusion-related reaction | 1 (1.1) | 0 | 1 (0.6) |
| Metabolism and nutrition disorders | 1 (1.1) | 1 (1.2) | 2 (1.1) |
| Steroid diabetes | 0 | 1 (1.2) | 1 (0.6) |
| Diabetic ketoacidosis | 1 (1.1) | 0 | 1 (0.6) |
| Psychiatric disorders | 0 | 1 (1.2) | 1 (0.6) |
| Suicide attempt | 0 | 1 (1.2) | 1 (0.6) |
| Renal and urinary disorders | 2 (2.2) | 0 | 2 (1.1) |
| Nephrotic syndrome | 1 (1.1) | 0 | 1 (0.6) |
| Renal failure | 1 (1.1) | 0 | 1 (0.6) |
| Skin and subcutaneous tissue disorders | 1 (1.1) | 0 | 1 (0.6) |
| Granuloma skin | 1 (1.1) | 0 | 1 (0.6) |

Notes: In summarizing n (%), if a patient had multiple events for a particular SOC or Preferred Term, the patient was counted only once for that SOC or Preferred Term. Results were sorted by Ravulizumab column in descending order of SOC percentage and then Preferred Term within SOC. AEs were coded using MedDRA version 24.0.

[a] One patient in the ravulizumab group experienced a clinical deterioration under the per protocol criteria of 'Significant symptomatic worsening' which was also reported as an SAE of MG crisis.

Abbreviations: AE = adverse event(s); COVID-19 = coronavirus disease 19; E = total number of events; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class

Other Serious Adverse Events During Ravulizumab Treatment Period Through the Data Cutoff Date

As of the 52-week data cutoff date, 27 (21.3%) patients in the Ravulizumab Treated Set had experienced 1 or more SAEs during ravulizumab treatment (Table ). Overall, 12 (9.4%) patients reported SAEs in the SOC of Infections and infestations and 6 (4.7%) patients reported SAEs in the SOC of Nervous system disorders.

For the patients in the RAV/RAV group who experienced SAEs, most SAEs occurred during the Randomized-Controlled Period; 4 patients who were treated with ravulizumab during the Randomized-Controlled Period had SAEs between > 6 to 12 months of ravulizumab treatment during the Open-Label Extension Period.

Five patients in the PBO/RAV group had SAEs after switching to ravulizumab during the Open-Label Extension Period. One patient had an SAE assessed as related to study drug during the Open-Label Extension Period which was due to "worsening of MG symptoms."

After the 52-week data cutoff date, 1 patient in the placebo group who switched to ravulizumab during the Open-Label Extension Period had a non-fatal SAE of meningitis (unknown aetiology). The patient had received meningococcal vaccination prior to study entry. The event was considered by the Investigator to be related to ravulizumab (compatible with partially treated bacterial meningitis). No action was taken with ravulizumab in response to this event and the patient continued to receive ravulizumab in the study.

**Table 42: Treatment-emergent Serious Adverse Events During the Ravulizumab Treatment Period Through the Data Cutoff Date (ALXN1210-MG-306 Ravulizumab Treated Set)**

| System Organ Class<br>Preferred term | Total | | |
|---|---|---|---|
| | 0 to 6 mo<br>(N = 127)<br>n (%) | > 6 to 12 mo<br>(N = 97)<br>n (%) | 0 to cutoff<br>(N = 127)<br>n (%) |
| Any SAE | 25 (19.7) | 5 (5.2) | 27 (21.3) |
| Infections and infestations | 10 (7.9) | 3 (3.1) | 12 (9.4) |
| COVID-19 | 1 (0.8) | 2 (2.1) | 2 (1.6) |
| COVID-19 pneumonia | 2 (1.6) | 0 | 2 (1.6) |
| Arthritis bacterial | 1 (0.8) | 0 | 1 (0.8) |
| Diverticulitis | 1 (0.8) | 0 | 1 (0.8) |
| Gangrene | 1 (0.8) | 0 | 1 (0.8) |
| Gastroenteritis viral | 1 (0.8) | 0 | 1 (0.8) |
| Herpes zoster | 1 (0.8) | 0 | 1 (0.8) |
| Infected skin ulcer | 1 (0.8) | 0 | 1 (0.8) |
| Pneumonia respiratory syncytial viral | 1 (0.8) | 0 | 1 (0.8) |
| Pneumonia viral | 0 | 1 (1.0) | 1 (0.8) |
| Staphylococcal sepsis | 1 (0.8) | 0 | 1 (0.8) |
| Suspected COVID-19 | 1 (0.8) | 0 | 1 (0.8) |
| Urinary tract infection | 1 (0.8) | 0 | 1 (0.8) |
| Nervous system disorders | 6 (4.7) | 0 | 6 (4.7) |
| Transient ischaemic attack | 2 (1.6) | 0 | 2 (1.6) |

**Table 42: Treatment-emergent Serious Adverse Events During the Ravulizumab Treatment Period Through the Data Cutoff Date (ALXN1210-MG-306 Ravulizumab Treated Set)**

| System Organ Class<br>Preferred term | Total | | |
|---|---|---|---|
| | 0 to 6 mo<br>(N = 127)<br>n (%) | > 6 to 12 mo<br>(N = 97)<br>n (%) | 0 to cutoff<br>(N = 127)<br>n (%) |
| Cerebral haemorrhage | 1 (0.8) | 0 | 1 (0.8) |
| Myasthenia gravis | 1 (0.8) | 0 | 1 (0.8) |
| Myasthenia gravis crisis | 1 (0.8) | 0 | 1 (0.8) |
| Syncope | 1 (0.8) | 0 | 1 (0.8) |
| General disorders and administration site conditions | 3 (2.4) | 1 (1.0) | 4 (3.1) |
| Asthenia | 1 (0.8) | 0 | 1 (0.8) |
| Chest pain | 0 | 1 (1.0) | 1 (0.8) |
| General physical health deterioration | 1 (0.8) | 0 | 1 (0.8) |
| Non-cardiac chest pain | 1 (0.8) | 0 | 1 (0.8) |
| Pyrexia | 1 (0.8) | 0 | 1 (0.8) |
| Injury, poisoning and procedural complications | 2 (1.6) | 1 (1.0) | 3 (2.4) |
| Lumbar vertebral fracture | 0 | 1 (1.0) | 1 (0.8) |
| Multiple fractures | 1 (0.8) | 0 | 1 (0.8) |
| Patella fracture | 1 (0.8) | 0 | 1 (0.8) |
| Musculoskeletal and connective tissue disorders | 3 (2.4) | 0 | 3 (2.4) |
| Intervertebral disc protrusion | 1 (0.8) | 0 | 1 (0.8) |
| Nodal osteoarthritis | 1 (0.8) | 0 | 1 (0.8) |
| Tendonitis | 1 (0.8) | 0 | 1 (0.8) |
| Respiratory, thoracic, and mediastinal disorders | 3 (2.4) | 0 | 3 (2.4) |
| Dyspnoea | 1 (0.8) | 0 | 1 (0.8) |
| Dyspnoea exertional | 1 (0.8) | 0 | 1 (0.8) |
| Lung infiltration | 1 (0.8) | 0 | 1 (0.8) |
| Eye disorders | 1 (0.8) | 1 (1.0) | 2 (1.6) |
| Cataract | 0 | 1 (1.0) | 1 (0.8) |
| Visual impairment | 1 (0.8) | 0 | 1 (0.8) |
| Gastrointestinal disorders | 2 (1.6) | 0 | 2 (1.6) |
| Dysphagia | 1 (0.8) | 0 | 1 (0.8) |
| Nausea | 1 (0.8) | 0 | 1 (0.8) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 2 (1.6) | 0 | 2 (1.6) |
| Squamous cell carcinoma of skin | 1 (0.8) | 0 | 1 (0.8) |
| Ureteral neoplasm | 1 (0.8) | 0 | 1 (0.8) |
| Cardiac disorders | 1 (0.8) | 0 | 1 (0.8) |
| Congestive cardiomyopathy | 1 (0.8) | 0 | 1 (0.8) |
| Metabolism and nutrition disorders | 1 (0.8) | 0 | 1 (0.8) |
| Steroid diabetes | 1 (0.8) | 0 | 1 (0.8) |
| Psychiatric disorders | 1 (0.8) | 0 | 1 (0.8) |
| Suicide attempt | 1 (0.8) | 0 | 1 (0.8) |

Note: The Ravulizumab Treated Set consisted of all patients who received at least 1 dose of ravulizumab either in the Randomized-Controlled Period or the Open-Label Extension Period. Per scope, only data during Randomized-Controlled Period were included for patients not expected to have Week 52 at data cutoff. This applied to both RAV/RAV and PBO/RAV patients. In summarizing n (%), if a patient had multiple events for a particular SOC or Preferred Term, the patient was counted only once for that SOC or Preferred Term. AEs were coded using MedDRA Version 24.0.

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 19; MedDRA = Medical Dictionary for Regulatory Activities; mo = months; SAE = serious adverse event; SOC = system organ class

**Deaths**

A total of 7 deaths occurred in the study by the time of 60-week CSR addendum (2 in the randomized control period and 5 in the Open Label Extension Period). None of the deaths were related to study drug by the Investigator. These deaths are summarized in the Table 43 below.

**Table 43: Deaths reported in Initial Clinical Study Report and 60-week Addendum Report from ALXN1210-MG-306 Study**

| Report | Preferred Term | Period from Study | Descriptive Summary |
|---|---|---|---|
| Clinical Study Report (primary analysis) | COVID-19 pneumonia | Randomized-Controlled Period | The patient had a medical history of gMG, arrhythmia, and diabetes mellitus, receiving prednisone, pyridostigmine, and azathioprine for gMG, was hospitalized with COVID-19 pneumonia on Day 163 of the Randomized-Controlled Period. On Day 163, the patient was transferred to the ICU and intubated. The patient was diagnosed with atrial fibrillation and worsening of hyperglycemia. On Day 178, the patient experienced staphylococcal sepsis. On Day 179, the patient died from respiratory and circulatory arrest during hospitalization due to COVID-19. |
| Clinical Study Report (primary analysis) | Cerebral hemorrhage | Randomized-Controlled Period | The patient had a medical history of gMG, atrial fibrillation, diabetes mellitus, hyperlipidemia, and hypertension, and was receiving corticosteroid and immunosuppressant treatment for gMG and edoxaban for treatment of atrial fibrillation. The patient was admitted to the hospital with diagnosis of cerebral hemorrhage on Day 138. The patient underwent endoscopic hematoma removal which was unsuccessful and suffered complications of continued bleeding and respiratory arrest and was intubated. On Day 142, a second surgery was performed which was also unsuccessful and on Day 145, the patient died due to cerebral hemorrhage. |
| Clinical Study Report (primary analysis) | COVID-19 | Open-Label Extension | The patient had a medical history of gMG, hypertension, hyperlipidemia, atrial septal defect, pre-diabetes, morbid obesity, and obstructive sleep apnea, receiving prednisone and mycophenolate mofetil for gMG. The patient was admitted to the hospital on Day 204 due to a COVID-19 infection. The patient had received ravulizumab during the Randomized-Controlled Period. On Day 216, the patient died due to COVID-19. |
| Clinical Study Report (primary analysis) | COVID-19 | Open-Label Extension | The patient had a medical history of gMG, atrial fibrillation, hyperlipidemia, hypertension, blood cholesterol increased, and sleep apnea, and was receiving prednisone and mycophenolate mofetil for gMG. The patient was admitted to the hospital due to COVID-19 on Day 174 of ravulizumab treatment during the Open-Label Extension Period. The patient had received placebo during the Randomized-Controlled Period. The patient died on Day 196 due to COVID-19 complications. |
| 60-week CSR addendum (reported after data cutoff) | COVID-19 | Open-Label Extension | The patient had a medical history of gMG and thymectomy, was receiving mycophenolate mofetil for gMG, and was admitted to the hospital because of COVID-19 on Day 355 of ravulizumab treatment during the Open-Label Extension Period. The patient died due to COVID-19 complications on Day 391 and had received placebo during the Randomized-Controlled Period. |
| 60-week CSR addendum (reported after data cutoff) | Toxicity to various agents | Open-Label Extension | The patient had a medical history of gMG with multiple comorbidities and was receiving pyridostigmine bromide treatment for gMG, gabapentin for generalized pain, and alprazolam for depression. The cause of death was listed as combined drug intoxication by drugs including fentanyl, gabapentin, and alprazolam taken at the same time and was indicated to be an accident. The patient had received placebo during the Randomized-Controlled Period. The patient died on Day 606 of the Open-Label Extension Period. |
| 60-week CSR addendum (reported after data cutoff) | Death | Open-Label Extension | The patient died on 23 Sep 2021 due to an unknown cause (autopsy report and death certificate were not provided). The last dose of ravulizumab was received on Day 251 (29 Mar 2021). The patient's last contact with the site was 26 Jun 2021 and was discontinued from the study due to physician decision on 08 Sep 2021. The patient also had SAEs of pneumonia, mitral valve stenosis, and vein rupture. |

### Adverse Events Related to COVID-19

During the Randomized-Controlled Period, 4 (4.5%) patients in the placebo group and 5 (5.8%) patients in the ravulizumab group had COVID-19 related AEs per the MedDRA v24.0 SMQ search of "COVID-19." None of these events was considered to be related to study drug by the Investigator.

As of the data cutoff date, 9 total patients in the Ravulizumab Treated Set experienced COVID-19 related AEs (ie, includes the 5 patients in the ravulizumab group who had COVID-19 related AEs during the Randomized-Controlled Period). However, upon additional medical review 1 of the 9 patients had an event of viral pneumonia which was not confirmed to be related to COVID-19. None of these events was considered to be related to study drug by the Investigator.

Six patients had COVID-19 related SAEs; however, upon additional medical review 1 of the 6 patients had an SAE of viral pneumonia which was not confirmed to be related to COVID-19. Three patients died during the study due to COVID-19; all 3 patients had multiple underlying risk factors for COVID-19 complications (such as metabolic, respiratory, and cardiovascular disease and obesity).

### *Laboratory findings*

There were no clinically significant changes in laboratory parameters in Study ALXN1210-MG-306 that were of safety concern.

- Vital signs, physical examination, and ECG: No safety signals were identified.
- Columbia-Suicidal Severity Rating Scale: None of the patients in the ravulizumab group had suicidal ideation or suicidal behavior at the timepoint of the C-SSRS evaluations during the Randomized-Controlled Period. Although suicidal ideation and/or suicidal behavior was not noted during the C-SSRS evaluation timepoints, it was noted that 1 patient in the ravulizumab group was hospitalized during the Randomized-Controlled Period due to a suicide attempt. This patient had a prior history of depression and suicide attempt; the SAE was considered not related to study drug by the Investigator.
- Pregnancy: No patients or partners became pregnant during the study.

## Immunogenicity

No treatment-emergent ADA-positive findings were observed after ravulizumab administration in any patients during the Randomized-Controlled Period. All assay results for antidrug neutralizing antibodies were negative.

### *Safety in special populations*

#### Intrinsic Factors

Analyses of the safety profile by intrinsic factors (ie, sex, race, age, geographic location) identified no sensitive subgroups that were considered to have an influence on the overall safety profile of ravulizumab..

#### Extrinsic Factors

Analyses of the safety profile by extrinsic factors (ie, immunosuppressant therapy use at baseline) identified no sensitive subgroups that were considered to have an influence on the overall safety profile of ravulizumab. Some extrinsic factors, including immunosuppressant therapy use, were included as categorical covariates in the population PK analysis.

### *Safety related to drug-drug interactions and other interactions*

No formal drug-drug interaction studies have been conducted with ravulizumab IV.

## *Discontinuation due to adverse events*

During the Randomized-Controlled Period, 3 (3.4%) patients in the placebo group and 2 (2.3%) patients in the ravulizumab group discontinued study drug due to AEs:

- 2 patients (placebo) discontinued study drug and withdrew from the study due to infusion-related reactions (1 SAE and 1 non-serious AE; both events were considered related to study drug by the Investigator)
- 1 patient (placebo) discontinued study drug due to non-serious back pain (not related to study drug) and withdrew from the study due to physician decision on Day 101.
- 1 patient (ravulizumab) discontinued study drug due to an SAE of infected skin ulcer (not related to study drug) and subsequently withdrew from the study on Day 153 due to physician decision
- 1 patient (ravulizumab) died due to COVID-19 pneumonia

As of the data cutoff date, 4 patients who received ravulizumab during the Randomized-Controlled Period had SAEs which led to discontinuation of study drug (includes the 2 patients in the ravulizumab group who had SAEs which led to discontinuation of study drug during the Randomized-Controlled Period as well as 2 patients in the ravulizumab group who died during ravulizumab treatment in the Open-Label Extension Period.

None of the patients who received placebo during the Randomized-Controlled Period discontinued study drug after switching to ravulizumab during the Open-Label Extension Period.

## *Post marketing experience*

The estimated postmarketing exposure to ravulizumab IV since the first Marketing Authorization (21 Dec 2018) through 30 Jun 2021 was 3996.7 PY for PNH and aHUS indications.

Meningococcal infection remains an important identified risk for ravulizumab IV based on the mechanism of action, findings from the ravulizumab clinical studies, and long-term experience with eculizumab (Soliris), another approved C5 complement inhibitor.

Three patients with PNH reported meningococcal infection in the postmarketing setting of ravulizumab (2 patients with serotype non-typeable and 1 patient with unknown serotype) with a reporting rate of approximately 0.08 per 100 PY [3 patients/3996.7 PY], between 197 to 322 days of the first dose of ravulizumab IV. Administration of a meningococcal vaccination at least 2 weeks prior to the administration of ravulizumab IV was confirmed in all 3 patients.

Long-term postmarketing experience with eculizumab showed consistent reporting rate of meningococcal infections in eculizumab-treated patients over the past 10 years at approximately 0.3 to 0.5 per 100 PY with the reporting rate for fatal outcomes at 0.03 per 100 PY representing 9.2% of patients who experienced meningococcal infections, similar to the proportion of fatal events in the general population among individuals with meningococcal infections (10% to 15%) (MacNeil, 2018[25]; Van Deuren, 2000[26]).

Additionally, hypersensitivity reactions were confirmed as an identified risk based on a cumulative data review of the Standardised MedDRA Query (SMQ) hypersensitivity

## 2.5.1. Discussion on clinical safety

The safety of ravulizumab in gMG has been evaluated in one Phase 3 study (Study ALXN1210 MG-306) which includes a placebo-controlled 26-week treatment period (completed) and a 2-year open label extension still ongoing. The primary analysis for Study 306 was conducted with a clinical cut-off date of 11 May 2021.

Overall, a total of 86 patients were exposed to ravulizumab in the Randomized-Controlled Period. These patients were treated with the proposed dosing regimen for a median duration of 25.6 weeks. Treatment compliance was 94.4% in the placebo group and 96.5% in the ravulizumab group.

The demographic and baseline characteristics were balanced between the placebo and ravulizumab groups.

Regarding the long-term safety profile, only 35 patients have been treated, for a period of 52 weeks. A such, the CHMP considered that the safety database presents limitations especially regarding less frequent or delayed events. However, given the low prevalence of Myasthenia Gravis, patient exposure is considered acceptable for the short-term safety assessment of ravulizumab.

The available safety information of ravulizumab in the already authorised indications (PNH, aHUS) can be taken as supportive taking into account that patients have been treated with the same dosing regimen. Study ALXN1210-MG-306 is expected to be completed (last patient's last visit) by 30 May 2023. The final clinical study report (CSR) will be available within 12 months from study completion (Q2 2024) and will be submitted once available.

An updated analysis of Study ALXN1210-MG-306 was performed and submitted during this application (data cut-off date 09 Nov 2021) that includes data through Week 60 for 169 patients.

The safety profile for ravulizumab was similar to that of placebo in adult patients with gMG during the 26-week Randomized-Controlled Period.

Most patients included in the Randomized–Controlled period reported AEs: 90.7% in the ravulizumab group vs. 86.5% in the placebo group. Of them, 33.7% of both ravulizumab- and placebo-treated patients reported AEs considered as related to study drug.

A total of 5 patients withdrew from study treatment due to AEs (3 on placebo, 2 on ravulizumab) during the double-blind period in Study MG-306. Three of them (1 on placebo, 2 on ravulizumab) were considered as serious. Two additional patients discontinued the treatment due to SAEs during the extension period.

During the Ravulizumab Treatment Period, 86.6% of patients experienced at least 1 AE. The percentage of patients reporting AEs was 35.1% during months 6 to 12 of ravulizumab treatment, compared to 85.8% during months 0 to 6 of ravulizumab treatment. The majority of AEs were considered to be not related to study drug,

During the Randomized-Controlled Period, headache, diarrhoea), and nausea were the most frequently reported AEs (≥ 10% of all patients).

Regarding adverse events through week 60, the most frequently reported AEs (≥ 10% of all patients) were headache and diarrhoea. A total of 58 (34.3%) patients reported AEs assessed as related to study drug by the Investigator. There was no trend towards increase in the incidence of AEs with longer-term

[25] MacNeil JR, Blain AE, Wang X, Cohn AC. Current Epidemiology and Trends in Meningococcal Disease-United States, 1996-2015. Clin Infect Dis. 2018 Apr 3;66(8):1276-1281.
[26] van Deuren M, Brandtzaeg P, van der Meer JW. Update on meningococcal disease with emphasis on pathogenesis and clinical management. Clin Microbiol Rev. 2000 Jan;13(1):144-66, table of contents.

exposure to ravulizumab and the safety profile has shown to remain consistent over time. The percentage of patients reporting AEs was 84.6%, 56.3%, and 30.7% during months 0 to 6, > 6 to 12, and > 12 to 18 of ravulizumab treatment, respectively. No new safety signals have emerged with longer exposure to ravulizumab

Injection-related reactions were reported in a similar rate by ravulizumab (32.6%) and placebo (31.5%). No relevant differences were observed between both groups.

No new adverse events have been reported in this new population. Overall, the AE profile is consistent with that known for ravulizumab in other indications.

The majority of the events were of mild or moderate severity. Severe events were reported by 16 of patients treated with ravulizumab (18.6%) vs. 14 (15.7%) of those on placebo.

More ravulizumab -treated patients experienced ≥1 SAE (23.3% ravulizumab vs.. 15.7% placebo), although most of them were considered as not related to the study drug. The most frequently reported SAEs were those related with infections and Nervous System disorders.

Life-threatening events were reported by 2 patients treated with ravulizumab (2.3%): arthritis bacterial (n = 1); and COVID-19 pneumonia (n = 1) vs. 1 (1.1%) of those on placebo: diabetic ketoacidosis (n = 1).

The incidence and nature of SAEs during the open-label period is similar to those reported during the double-blind period. The most frequently reported AEs were headache (16.6%), diarrhoea (13.6%), nausea (9.5%), back pain (9.5%), fatigue (9.5%), nasopharyngitis (8.9%), urinary tract infection (8.9%), arthralgia (8.9%), dizziness (8.3%), abdominal pain (5.3%) COVID-19 (5.3%) and upper respiratory tract infection (5.3%). No clear safety signals were identified. All AEs mentioned above were already reflected in the PI with the exception of COVID-19 and urinary tract infections. Regarding the urinary infections reported it was explained that the differences between groups were driven by one patient, that all patients reporting urinary infections had other predisposing risk factors and that the incidence did not increase with longer exposure to ravulizumab.

Around 21% of patients reported at least a SAE. The most frequently reported were those related to infections (9.4%) and nervous system disorders (4.7%).

A total of 7 deaths occurred in the study but none were related to study drug by the investigator.

Only meningococcal infections were included as Adverse events of special interest. No events were reported during the analysed period. However, after the 52-week data cutoff date, 1 patient in the placebo group who switched to ravulizumab during the Open-Label Extension Period had a non-fatal SAE of meningitis of unknown aetiology. The patient had received meningococcal vaccination prior to study entry. The event was considered by the Investigator to be related to ravulizumab (compatible with partially treated bacterial meningitis). No action was taken with ravulizumab in response to this event and the patient continued to receive ravulizumab in the study.

Regarding the safety profile in special populations, subgroup analyses were performed by sex, race, age, geographic location. No relevant differences were detected between different subgroups. However, results for some of the subgroups should be interpreted with caution given the small number of patients. With respect to drug-drug interactions no specific studies were conducted, the subgroup analysis by immunosuppressant therapy used at baseline did not show any relevant safety signal.

No clinically significant changes in the laboratory results, vital signs, physical examinations, and electrocardiograms were observed.

The postmarketing global data by the data cut-off date of 30 Jun 2021 do not seem to show any new safety concern.

### 2.5.2. Conclusions on clinical safety

The safety database of ravulizumab in the approved indication is considered limited both in terms of the number of exposed patients and the duration of the exposure. However, the small size of the safety database is not unexpected considering the rarity of the condition.

Given the low prevalence of Myasthenia Gravis, patient exposure is considered acceptable for the short-term safety assessment of ravulizumab.

As for the long-term safety profile the extension study is ongoing.

Overall, the reported AE profile is consistent with that known for ravulizumab in other indications, with no unexpected findings.

CHMP considered that the available safety data supports the use of ravulizumab in the approved indication.

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4 with the following content:

### *Safety concerns*

| Summary of Safety Concerns | |
|---|---|
| Important identified risks | Meningococcal infection |
| Important potential risks | Serious haemolysis after drug discontinuation in PNH patients<br>Severe TMA complications in aHUS patients after ravulizumab discontinuation<br>Immunogenicity<br>Serious infections<br>Malignancies and haematologic abnormalities in PNH patients |
| Missing information | Use in pregnant and breast-feeding women |

Abbreviations: aHUS = atypical haemolytic uraemic syndrome; PNH = paroxysmal nocturnal haemoglobinuria; TMA = thrombotic microangiopathy.

## *Pharmacovigilance plan*

| Study/Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 3** – required additional pharmacovigilance activities | | | | |
| "A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Complement Inhibitor-Naïve Adult Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)"<br>(ALXN1210-PNH-301)<br>Ongoing | To evaluate the safety and efficacy of ALXN1210 administered by intravenous infusion to adult patients with PNH who are naïve to complement inhibitor treatment<br>To collect and evaluate safety data specific to the use of ULTOMIRIS and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in treated PNH patients | Meningococcal infection<br>Serious haemolysis after drug discontinuation in PNH patients<br>Immunogenicity<br>Serious infections<br>Malignancies and haematologic abnormalities in PNH patients<br>Use in pregnant and breast-feeding women | Final CSR | Oct 2023 |
| "A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated with Eculizumab"<br>(ALXN1210-PNH-302)<br>Ongoing | To collect and evaluate efficacy and safety data specific to the use of ULTOMIRIS and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in treated PNH patients | Meningococcal infection<br>Serious haemolysis after drug discontinuation in PNH patients<br>Immunogenicity<br>Serious infections<br>Malignancies and haematologic abnormalities in PNH patients<br>Use in pregnant and breast-feeding women | Final CSR | Dec 2022 |

| Study/Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| "Paroxysmal Nocturnal Hemoglobinuria (PNH) Registry"<br>M07-001<br>Ongoing | To collect and evaluate safety data specific to the use of SOLIRIS / ULTOMIRIS and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in SOLIRIS / ULTOMIRIS and non-SOLIRIS / ULTOMIRIS treated patients. | Meningococcal infection<br>Serious haemolysis after drug discontinuation in PNH patients<br>Serious infections<br>Malignancies and haematologic abnormalities in PNH patients<br>Use in pregnant and breast-feeding women | Interim data analysis | Every 2 years interim data analysis report |
| "Atypical Hemolytic Uremic Syndrome (aHUS) Registry"<br>(M11-001)<br>Ongoing | To collect and evaluate safety and effectiveness data specific to the use of eculizumab / ravulizumab in aHUS patients<br>To assess the long-term manifestations of TMA complications of aHUS as well as other clinical outcomes, including mortality and morbidity in aHUS patients receiving eculizumab / ravulizumab treatment or other disease management. | Meningococcal infection<br>Severe TMA complications in aHUS patients after ravulizumab discontinuation<br>Immunogenicity<br>Serious infections<br>Use in pregnant and breast-feeding women | Interim data analysis | Every 2 years interim data analysis report |
| "Single Arm Study of ALXN1210 in Complement Inhibitor Treatment-Naïve Adult and Adolescent Patients with Atypical Hemolytic Uremic Syndrome (aHUS)"<br>(ALXN1210-aHUS-311)<br>Ongoing | To assess the efficacy and long-term safety of ravulizumab in complement inhibitor treatment-naïve adolescent and adult patients with aHUS to inhibit complement-mediated TMA as characterised by thrombocytopenia, haemolysis, and renal impairment | Meningococcal infection<br>Severe TMA complications in aHUS patients after ravulizumab discontinuation<br>Immunogenicity<br>Serious infections<br>Use in pregnant and breast-feeding women | Final CSR | Dec 2023 |

## *Risk minimisation measures*

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Meningococcal infection | Routine risk minimisation measures<br>– SmPC sections 4.3, 4.4, and 4.8<br>– PL sections 2 and 4<br>Recommendations for vaccination/antibiotic prophylaxis in SmPC section 4.4 and PL section 2<br>Signs and symptoms of meningococcal infections listed in SmPC section 4.4 and PL section 2<br>Restricted medical prescription<br>Additional risk minimisation measures<br>Educational materials<br>– PNH/aHUS/gMG Physician's Guide<br>– PNH/aHUS/gMG Patient's Information Brochure<br>– PNH/aHUS Parent's Information Brochure<br>– Patient card<br>Controlled distribution<br>Revaccination reminder | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>– Specific adverse reaction follow-up questionnaire<br>Additional pharmacovigilance activities:<br>– Study ALXN1210-PNH-301 (final study report date: Oct 2023)<br>– Study ALXN1210-PNH-302 (final study report date: Dec 2022)<br>– PNH registry (M07-001)<br>– aHUS registry (M11-001)<br>– Study ALXN1210-aHUS-311 (final study report date: Dec 2023) |
| Serious haemolysis after drug discontinuation in PNH patients | Routine risk minimisation measures<br>– SmPC section 4.4<br>– PL section 3<br>Monitoring of patients who discontinued ULTOMIRIS recommended in SmPC section 4.4 and PL section 3<br>Additional risk minimisation measures<br>Educational materials<br>– PNH Physician's Guide<br>– PNH Patient's Information Brochure<br>– PNH Parent's Information Brochure | Additional pharmacovigilance activities:<br>– Study ALXN1210-PNH-301 (final study report date: Oct 2023)<br>– Study ALXN1210-PNH-302 (final study report date: Dec 2022)<br>– PNH registry (M07-001) |
| Severe TMA complications in aHUS patients after ravulizumab discontinuation | Routine risk minimisation measures<br>– SmPC section 4.4<br>Additional risk minimisation measures<br>Educational materials<br>– aHUS Physician's Guide<br>– aHUS Patient's Information Brochure<br>– aHUS Parent's Information Brochure | Additional pharmacovigilance activities:<br>– aHUS registry (M11-001)<br>– Study ALXN1210-aHUS-311 (final study report date: Dec 2023) |

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Immunogenicity | Routine risk minimisation measures<br>– SmPC sections 4.4 and 4.8<br>Additional risk minimisation measures<br>Educational materials<br>– PNH/aHUS/gMG Physician's Guide<br>– PNH/aHUS/gMG Patient's Information Brochure<br>– PNH/aHUS Parent's Information Brochure | Additional pharmacovigilance activities:<br>– Study ALXN1210-PNH-301 (final study report date: Oct 2023)<br>– Study ALXN1210-PNH-302 (final study report date: Dec 2022)<br>– aHUS registry (M11-001)<br>– Study ALXN1210-aHUS-311 (final study report date: Dec 2023) |
| Serious infections | Routine risk minimisation measures<br>– SmPC sections 4.3, 4.4 and 4.8<br>– PL sections 2, 3 and 4<br>Recommendations for vaccination of paediatric patients against *Haemophilus influenzae* and pneumococcal infections in SmPC section 4.4 and PL section 2.<br>Additional risk minimisation measures<br>Educational materials<br>– PNH/aHUS/gMG Physician's Guide<br>– PNH/aHUS/gMG Patient's Information Brochure<br>– PNH/aHUS Parent's Information Brochure | Additional pharmacovigilance activities:<br>– Study ALXN1210-PNH-301 (final study report date: Oct 2023)<br>– Study ALXN1210-PNH-302 (final study report date: Dec 2022)<br>– PNH registry (M07-001)<br>– aHUS registry (M11-001)<br>– Study ALXN1210-aHUS-311 (final study report date: Dec 2023) |
| Malignancies and haematologic abnormalities in PNH patients | Routine risk minimisation measures<br>None proposed<br>Additional risk minimisation measures:<br>– PNH Physician's Guide<br>– PNH Patient's Information Brochure<br>– PNH Parent's Information Brochure | Additional pharmacovigilance activities:<br>– Study ALXN1210-PNH-301 (final study report date: Oct 2023)<br>– Study ALXN1210-PNH-302 (final study report date: Dec 2022)<br>– PNH registry (M07-001) |

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Use in pregnant and breast-feeding women | Routine risk minimisation measures<br>– SmPC sections 4.6 and 5.3<br>– PL section 2<br>Recommendations on contraception in SmPC section 4.8 and PL section 2<br>Additional risk minimisation measures<br>Educational materials<br>– PNH/aHUS/gMG Physician's Guide<br>– PNH/aHUS/gMG Patient's Information Brochure | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>– Specific adverse reaction follow-up questionnaire<br>Additional pharmacovigilance activities:<br>– Study ALXN1210-PNH-301 (final study report date: Oct 2023)<br>– Study ALXN1210-PNH-302 (final study report date: Dec 2022)<br>– PNH registry (M07-001)<br>– aHUS registry (M11-001)<br>– Study ALXN1210-aHUS-311 (final study report date: Dec 2023) |

Abbreviations: aHUS = atypical haemolytic uraemic syndrome; gMG = generalised myasthenia gravis, PNH = paroxysmal nocturnal haemoglobinuria; PL = package leaflet; SmPC = summary of product characteristics.

### *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

#### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Ultomiris 300 mg/ 30 mL concentrate for solution for infusion (parent leaflet). The bridging report submitted by the MAH has been found acceptable.

## 3. Benefit-Risk Balance

### *3.1. Therapeutic Context*

#### 3.1.1. Disease or condition

The approved indication for Ultomiris is:

"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."

Myasthenia gravis (MG) is a rare complement-mediated autoimmune disease characterised by the production of autoantibodies targeting proteins located at the neuromuscular junction. The most common target of autoantibodies in gMG is the nicotinic acetylcholine receptor (AChR).

Patients with gMG present with muscle weakness that characteristically becomes more severe with repeated use and recovers with rest. Muscle weakness can be localised to specific muscles, but often progresses to more diffuse muscle weakness[27,28,29]. Generalised myasthenia gravis symptoms can become life-threatening when muscle weakness involves muscles that are responsible for breathing. The most dangerous complication of gMG, known as myasthenic crisis, requires hospitalisation, intubation, and mechanical ventilation. Approximately 15% to 20% of patients with gMG will experience a myasthenic crisis within 2 years of diagnosis[30].

### 3.1.2. Available therapies and unmet medical need

Most therapies for gMG focus on either augmenting the AChR signal or non-specifically suppressing the autoimmune response. First-line therapy for symptomatic gMG is treatment with acetylcholinesterase (AChE) inhibitors and in patients who remain symptomatic, corticosteroids with or without systemic immunosuppressants are used off-label. Immunosuppressants used frequently in gMG include azathioprine and mycophenolate mofetil. Cyclosporine, methotrexate, tacrolimus, cyclophosphamide, and rituximab are also used occasionally. Intravenous immunoglobulin (IVIG) and plasma exchange (PLEX) are typically used short-term to manage worsening MG symptoms and in patients with myasthenic crisis or life-threatening signs such as respiratory insufficiency or dysphagia [31, 32]. Eculizumab, a monoclonal antibody, has been approved for the treatment of refractory generalized myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive.

### 3.1.3. Main clinical studies

Clinical evidence supporting the new indication is primarily based on the ongoing Study ALXN1210-MG-306. Study ALXN1210 MG 306 is a Phase 3, randomized, double-blind, parallel-group, placebo controlled, 26-week multicenter study with an ongoing open-label extension to evaluate the safety and efficacy of ravulizumab (n=86) administered by IV infusion compared to placebo (n=89) in adult patients with gMG.

The study consists of an up to 4-week Screening Period, a 26 week double-blind, Randomized Controlled Period, and an Open-Label Extension Period of up to 2 years. Patients were treated on a body weight-based posology receiving a loading dose of 2400-3000 mg followed by maintenance doses of 3000 -3600 mg on Day 15 and then every 8 weeks (q8w). This dosing regimen is identical to that approved for the treatment of PHN and aHUS.

## *3.2. Favourable effects*

Study MG-306 met its primary endpoint (change from Baseline in MG-ADL total score at Week 26 of the Randomized-Controlled Period). Patients treated with ravulizumab showed significantly better control of MG symptoms than those who received placebo on the subjective assessment by the patient (MG-ADL).

[27] Chamanza R, Marxfeld HA, Blanco AI, Naylor SW, Bradley AE. Toxicol Pathol.2010;38(4):642-57.
[28] Gilhus NE, Verschuuren JJ. Lancet Neurol. 2015;14(10):1023-36.
[29] Gilhus NE. N Engl J Med. 2016;375(26):2570-2581.
[30] Ramizuddin, M. IOSR J Dent Med Sci. 2014;13(7):67-97
[31] Riedemann NC, Guo RF, Laudes IJ, et al. FASEB J. 2002;16(8):887-8.
[32] Sanders DB, Wolfe GI, Benatar M, et al. Neurology. 2016;87(4):419-25.

At Week 26 the mean difference between the treatment arms was -1.6 (95% CI -2.6, -0.7; p = 0.0009). This was supported by sensitivity analyses in the PP population as well as by supplemental analyses for the primary endpoint.

The secondary endpoints, also assessed changes from baseline to Week 26, included the change in the Quantitative Myasthenia Gravis (QMG) total score, the proportion of patients with improvements of at least 5 and 3 points in the QMG and MG-ADL total scores, respectively, as well as changes in quality-of-life assessments.

The quantitative evaluation of relevant muscle groups by the physician (QMG) measured as secondary endpoint also showed a statistically significant difference between ravulizumab and placebo. The LS mean (SEM) reduction from Baseline to Week 26 in QMG total score was -2.0 [0.59]; 95% CI: -3.2, -0.8; p = 0.0009).

A numerically greater effect was observed in the QoL MG scales (change in MG-QOL15r score, change in Neuro-QoL fatigue scale) favouring ravulizumab although according to testing hierarchy, they did not reach statistical significance. The LS mean (SEM) reduction from Baseline to Week 26 in MG-QoL15r total score was -1.7 [0.7]; 95% CI: -3.4, 0.1; p=0.0636.

The LS mean (SEM) reduction from Baseline to Week 26 in Neuro-QoL Fatigue score was -2.2; 95% CI: -6.9, 2.6; p=0.3734.

30% of patients on ravulizumab had ≥ 5 point reduction in the QMG total score compared with 11.3% placebo (OR 3.350 [95% CI 1.443, 7.777]; p=0.0052).

In addition, more patients in the ravulizumab group (56.7%) compared to placebo group (34.1%) achieved a ≥3-point reduction, although this analysis was not considered (formally) statistically significant according to the prespecified hierarchical testing for secondary endpoints. MG Composite Scale results are in line with those observed for MG-ADL score and QMG scales. Patients treated with both ravulizumab and with placebo experienced a reduction in the scores (ravulizumab -6.1 [0.73], placebo -3.2 [0.71]). The difference was statistically significant (-2.9 [0.93]; 95% CI: -4.8, -1.1; p = 0.0019).

Patients in the ravulizumab arm suffered fewer clinical deteriorations (10 [11.6%] vs. 18 [20.2%]) or rescue therapy (8 [9.3%] vs. 14 [15.7%]) than the patients in the placebo arm during the study. Similarly, fewer patients on ravulizumab needed hospitalization due to MG during the 26 week period of treatment compared to placebo (7 [8%] vs. 3 [3%]).

Maintenance of the effect of ravulizumab beyond 6-month treatment is based on the still ongoing open label period, where all patients involved in Study MG-306 are treated with ravulizumab and followed up to 2 years. An update of the Study MG-306 with a clinical database cut-off date of 09 Nov 2021 was provided during this application. Additional data from the 161 patients who received 1 or more doses of ravulizumab in the extension period collected up to the Week 60 visit in the Open-Label Extension Period have been provided. All patients received treatment with ravulizumab during the Open-Label Extension Period, including patients randomized to ravulizumab and patients randomized to placebo during the Randomized-Controlled Period (RAV/RAV and PBO/RAV group, respectively). When patients who received placebo in the randomized controlled period were treated with ravulizumab in the open-label extension period an improvement similar to that showed by patients on active treatment in the previous study was observed. In patients previously treated with ravulizumab, the response was maintained.

During this phase of the clinical trial background therapy could be adjusted. In this period 50.3% of patients had a change in concomitant MG medication. The most common change was a decrease in

corticosteroids for systemic use due to MG symptoms improved (20.7%) with 11 (6.5%) patients discontinuing corticosteroids for systemic use.

## *3.3. Uncertainties and limitations about favourable effects*

The magnitude of the effect regarding the primary endpoint was questioned by CHMP. CHMP considered that the statistically significant reduction experienced in symptoms of 1.6 points in the mean change in MG-ADL score (primary endpoint) with respect to baseline during the randomized controlled period was modest. This also applied to the observed findings in the main secondary endpoints, when they were expressed in terms of absolute changes of the respective scales.

The clinical relevance of the treatment effect was questioned based on the fact that it did not achieve the accepted thresholds for clinical meaningfulness for the utilized scales established in literature (i.e. MCID of 2 point[33],[34]).

CHMP considered that these thresholds should be used for individual responder analyses and not as a reference point for a population-average drug-placebo treatment effect. Admittedly, this criterion could be considered as a cut-off value in responder analysis, as this is based on an "individual level" approach. In this respect 63.9% of patients treated with ravulizumab and 53.0% of patients treated with placebo showed a 2-point reduction in MG-ADL score, being the reported 10.9% difference of difficult interpretation. Moreover, the measured difference between ravulizumab and placebo did not achieve the treatment effect of 1.9 points on the MG-ADL score used at the planning stage.

An estimation of the effect size for the primary and secondary endpoints (MG-ADL and QMG scales) was provided in order to inform about the magnitude of treatment effects, showing an Hedge's g effect size of -0.49 and -0.50, respectively, which is defined as a moderate effect.

From the patient perspective (QoL measures), the changes MG-QOL15r score and in Neuro-QoL fatigue scale were not statistically significant even if results numerically favoured ravulizumab compared to placebo.

As it was reflected also by the inclusion criteria on prior/concomitant medications, in the ravulizumab study 306, gMG patients of lower disease severity were also included.

## *3.4. Unfavourable effects*

In the Randomized-Controlled Period headache, diarrhoea and nausea were the most frequently reported AEs (≥ 10% of all patients). Overall, the AE profile is consistent with that known for ravulizumab in other indications.

More ravulizumab -treated patients experienced ≥1 SAE (23.3% ravulizumab vs. 15.7% placebo), although most of them were considered as not related to the study drug. The most frequently reported SAEs were those related with infections (8.1% of patients treated with ravulizumab, 4.5% of patients treated with placebo); and Nervous System disorders (5.8% of patients treated with ravulizumab, 4.5% of patients treated with placebo).

In the Ravulizumab Treated Set 88.8% of patients reported AEs (related AEs 34.3%). No additional safety issues were identified with prolonged and repeated administration of ravulizumab. As for the

[33] Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. Neurology. 1999;52(7):1487-9.
[34] Muppidi S, Wolfe GI, Conaway M, Burns TM. MG-ADL: still a relevant outcome measure. Muscle Nerve. 2011;44(5):727-31.

long-term safety profile the most frequently reported AEs were headache (16.6%), diarrhoea (13.6%), nausea (9.5%), back pain (9.5%), fatigue (9.5%), nasopharyngitis (8.9%), urinary tract infection (8.9%), arthralgia (8.9%), dizziness (8.3%), abdominal pain (5.3%) COVID-19 (5.3%) and upper respiratory tract infection (5.3%).

No meningococcal infections were reported during the analysed period. After the 52-week data cut-off date, 1 patient in the placebo group who switched to ravulizumab had a non-fatal SAE of meningitis of unknown aetiology during the Open-Label Extension Period.

Seven deaths have been reported in the total ravulizumab group. None of the fatal events were considered by the investigator to be related to ravulizumab treatment.

## *3.5. Uncertainties and limitations about unfavourable effects*

Overall, a total of 86 patients were exposed to ravulizumab in the Randomized-Controlled Period. These patients were treated with the proposed dosing regimen for a median duration of 25.6 weeks. Treatment compliance was 94.4% in the placebo group and 96.5% in the ravulizumab group. A such, the CHMP considered that the safety database presents limitations especially regarding less frequent or delayed events.

## *3.6. Effects Table*

**Effects Table for Ultomiris (ravulizumab) for the treatment of adult patients with AChR antibody-positive gMG with remaining symptomatology despite at least one immunomodulatory therapy (data cut-off: 11 May 2021) - Study ALXN1210-MG-306**

| Effect | Short description | Unit | Ravulizumab | Placebo | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| **Primary endpoint** MG-ADL | Change from Baseline in MG-ADL Total Score | LS mean (SEM) | -3.1 (0.38) | -1.4 (0.37) | Treatment Effect -1.6 (95% CI: -2.6, -0.7) P-value 0.0009 Difference < 2 points (MCDI) | Study ALXN1210-MG-306 |
| **Second endpoint 1** QMG Total Score | Change from Baseline in QMG Total Score | LS mean (SEM) | -2.8 (0.46) | -0.8 (0.45) | Treatment Effect -2.0 (95% CI: -3.2, -0.8) P-value 0.0009 Difference < 3 points (MCDI) | Study MG-306 |
| **Second endpoint 2** QMG responder rate | QMG ≥5-point improvement | % | 30.0% | 11.3% | OR 3.350 (95% CI: 1.443 , 7.777) P-value 0.0052 | Study MG-306 |
| **Second endpoint 3** MG-QOL15r | Change from Baseline in MG-QOL15r Score | LS mean (SEM) | -3.3 (0.71) | -1.6 (0.70) | Treatment Effect -1.7 (95% CI: -3.4 , 0.1) P-value 0.0636 | Study MG-306 |
| **Second endpoint 4** Neuro-QOL-fatigue | Change from Baseline in Neuro-QOL-fatigue Score | LS mean (SEM) | -7.0 (1.92) | -4.8 (1.87) | Treatment Effect -2.2 (95% CI: (-6.9 , 2.6) P-value 0.3734 (Nominal p-values) | Study MG-306 |
| **Second endpoint 5** MG-ADL responder rate | MG-ADL ≥3-point improvement | % | 56.7% | 34.1% | OR 2.526 (95% CI: 1.330 , 4.799) P-value 0.0049 (Nominal p-values) | Study MG-306 |
| **Unfavourable Effects** | | | | | | |
| AEs | Incidence of AEs regardless of causality | n (%) | 78 (90.7) | 77 (86.5) | | Study ALXN1210-MG-306 RCP |
| Related AEs | Proportion | n (%) | 29 (33.7) | 30 (33.7) | | Study MG-306 RCP |
| SAEs | Incidence of serious | n (%) | 20 (23.3) | 14 (15.7) | | Study MG-306 RCP |

| Effect | Short description | Unit | Ravulizumab | Placebo | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| | adverse events | | | | | |
| Death | Proportion | n (%) | 2 (2.3) | 0 | | Study MG-306 RCP |
| AEs | Incidence of AEs regardless of causality | n (%) | 110 (86.6) | | | Study MG-306 RTS |
| Related AEs | Proportion | n (%) | 43 (33.9) | | | Study MG-306 RTS |
| SAEs | Incidence of serious adverse events | n (%) | 27 (21.3) | | | Study MG-306 RTS |
| Death | Proportion | n (%) | 4 (3.1) | | | Study MG-306 RTS |
| Headache | Common TEAE | n (%) | 16 (18.6) | 23 (25.8) | | Study MG-306 RCP |
| Diarrhoea | Common TEAE | n (%) | 13 (15.1) | 11 (12.4) | | Study MG-306 RCP |
| Nausea | Common TEAE | n (%) | 9 (10.5) | 9 (10.1) | | Study MG-306 RCP |
| Dizziness | Common TEAE | n (%) | 8 (9.3) | 3 (3.4) | | Study MG-306 RCP |
| Back pain | Common TEAE | n (%) | 7 (8.1) | 5 (5.6) | | Study MG-306 RCP |
| Arthralgia | Common TEAE | n (%) | 6 (7.0) | 7 (7.9) | | Study MG-306 RCP |
| Fatigue | Common TEAE | n (%) | 6 (7.0) | 6 (6.7) | | Study MG-306 RCP |
| Abdominal pain | Common TEAE | n (%) | 5 (5.8) | 0 | | Study MG-306 RCP |

Abbreviations: CI= Confidence Interval, LS = Least Squares; MG-ADL=MG Activities of Daily Living total score, MG-QoL15r= Revised 15-Component Myasthenia Gravis Quality of Life, MMRM = mixed-effect model for repeated measures; Neuro-QOL-fatigue = Neurological Quality of Life Fatigue, QMG = Quantitative MG total score, SEM = Standard Error of Mean, RCP= Randomized-Controlled Period, RTS= Ravulizumab Treated Set

Notes: Secondary efficacy endpoints were tested in a hierarchical approach (numbers included for testing order). Hierarchical testing proceeded from 1 to 5, and if statistical significance was not achieved (p-value > 0.05), then subsequent endpoints were not considered statistically significant and all displayed p-values from analyses of lower hierarchy were to be considered nominal.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Generalized Myasthenia Gravis is associated with relevant disability due to muscle weakness and fatigue of fluctuating course especially in patients with at least moderate condition. Treatment is aimed to control the symptoms and the underlying immune dysregulation. With respect to the structurally related eculizumab (administered every 2 weeks) ravulizumab allows a reduction in the frequency of infusions. It represents a reduced treatment burden, which is of value for the patients usually requiring numerous other treatments in the context of a chronic disease.

Overall, ravulizumab has shown an effect over placebo on the control of symptoms assessed by the patient (MG-ADL score, primary endpoint) and by the physician (QMG score; secondary endpoint) in a population with an established, advanced condition of moderate severity in spite of concomitant MG therapy. This is consistent with MGC score results, a scale derived from the other two scales.

While the magnitude of a clinically relevant effect could be questioned, the totality of the evidence should be considered when concluding on the efficacy of ravulizumab. In this respect the observed treatment effects are consistent across the responder rates reported both from the patient's (≥ 3-point reduction in MG-ADL total score) and physician's perspective (≥ 5 point reduction in the QMG total

score). It should also be mentioned that more stringent criteria (i.e. greater point reduction thresholds) led to more clear differences between the ravulizumab and the placebo groups.

Supportive evidence derives also from the clinical impact of ravulizumab in the course of the disease. Ravulizumab treated patients experienced less clinical deterioration, less MG-related hospitalization and required less rescue therapy than placebo treated patients. However, the interpretation of these outcomes is limited by the reduced numbers of events by group and the exploratory nature of the endpoints. However, a consistent response has been shown in the scales measured, which reinforces the observed effect. During the extension period, where changes in background therapy were allowed, 50.3% of patients had a change in concomitant MG medication. The most common change was a decrease in corticosteroids for systemic use due to MG symptoms improved (20.7%) with 11 (6.5%) patients discontinuing corticosteroids for systemic use.

Maintenance of the effect of ravulizumab beyond 6-month treatment is based on the still ongoing open label period, where all patients involved in Study MG-306 are treated with ravulizumab and followed up to 2 years. With the limitations given by the open label design and the fact that the study is still ongoing, the maintenance of the effect is considered sufficiently established. The final results of the study will be submitted once available.

The safety database of ravulizumab in the proposed indication is considered limited in terms of the number of exposed patients. The updated analysis of Study ALXN1210-MG-306 performed (data cut-off date 09 Nov 2021) includes data from 169 patients through Week 60.

The small size of the safety database is not unexpected considering the rarity of the condition. Overall, the reported AE profile is consistent with that known for ravulizumab in other indications. No additional safety issues were identified with prolonged and repeated administration of ravulizumab.

The extension study is ongoing. The MAH should submit the final results when available in order to complete the long-term efficacy and safety assessment.

## 3.7.2. Balance of benefits and risks

Ravulizumab has shown an effect over placebo on the control of symptoms assessed by the patient and by the physician. Whereas some uncertainties still remain (e.g. what treatment effect size with respect to placebo is to be considered clinically relevant) the totality of data submitted supports the conclusion that efficacy has been sufficiently demonstrated to support the use of ravuzilumab in the approved indication.

Long-term efficacy is based on the effect of ravulizumab during the open label extension period of the study, still ongoing. With the limitations given by the open label design and the fact that the study is still ongoing, the maintenance of the effect is considered sufficiently supported.

The observed safety profile of ravulizumab per se does not raise any severe or unexpected concerns and it is consistent with that known for ravulizumab in other indications; it is noted, however, that the conclusions are based on a very limited safety database.

As for the wording of the indication CHMP considered that taking into account that eculizumab and ravulizumab are structurally similar, do share the same mechanism of action and that the design of study ECU-MG-301, which supported approval of eculizumab for the treatment of refractory generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody-positive, was similar to that of the ravulizumab MG-306 study, the same indication wording as the one for Soliris could be considered adequate also for ravulizumab. However further justification was provided that demonstrated that there are several differences between the population included in

the eculizumab study (Study ECU-MG-301) and that included in the ravulizumab study (Study ALXN1210-MG-306). In general, patients included in eculizumab study seem to correspond to a more severe, more heavily treated population, in accordance to the requirement of having failed to at least 2 previous treatments and the approved indication in a refractory population.

Whereas the fact that ravulizumab and eculizumab share biochemical structure, mechanism of action and target population would favour granting a similar therapeutic indication, the differences in the population in whom the efficacy and safety data have been obtained would justify a different wording. This does not necessary mean that the effect of both medicinal products differs from each other but that the therapeutic indication is adjusted to the available evidence.

Considering the above, granting a broader indication to ravulizumab seems justified. As such, the final approved indication for ravulizumab is:

"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."

Regarding the claim for an additional year of market protection submitted by the MAH, it is considered that Ultomiris in the claimed indication brings a significant clinical benefit over existing therapies based on an improved efficacy compared to acetylcholinesterase inhibitors, corticosteroids and azathioprine, and a major contribution to patient care compared to Soliris (based on a reduced treatment burden with approximately 7 infusions for ravulizumab versus 26 infusions for eculizumab annually).

### 3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

## *3.8. Conclusions*

The overall B/R of Ultomiris is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include treatment of adult patients with generalized myasthenia gravis (gMG). As a consequence, Sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 and 6.6 of the SmPC and corresponding sections in the Package Leaflet are updated accordingly. The RMP has been updated to version 4.0 to align with the indication extension. Lastly, the minor editorial corrections are made throughout the SmPc and package leaflet. The Applicant also requested 1 year of market protection for

a new indication (Article 14(11) of Regulation (EC) 726/2004).

### *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

### *Similarity with authorised orphan medicinal products*

The CHMP by consensus is of the opinion that Ultomiris is similar to Soliris and not similar to Vygart within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

### *Derogation(s) from market exclusivity*

The CHMP by consensus is of the opinion that pursuant to Article 8 of Regulation (EC) No. 141/2000 the following derogation laid down in Article 8.3 of the same Regulation apply:

the holder of the marketing authorisation for Soliris has given his consent to the MAH.

### *Additional market protection*

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

## 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

### *Scope*

Please refer to the Recommendations section above.

### *Summary*

Please refer to Scientific Discussion: EMEA/H/C/004954/II/0026