1. SYNOPSIS

Study 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 Number: ALXN1210-MG-306

Regulatory Agency Identifier Number(s):

IND Number	140115
EudraCT Number	2018-003243-39

Study Phase: 3

Name of Study Intervention: Ravulizumab (ALXN1210) intravenous (IV)

Trade Name: ULTOMIRIS®

Name of Sponsor/Company: Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard Boston, MA 02210 USA

Number of Study Center(s) and Countries:

This study was conducted at 179 centers that enrolled participants in North America, Europe, Asia-Pacific, and Japan.

Publications (if any):

Bril V, Shin J, Silverstri N, et al. Ravulizumab in Adults with Generalized Myasthenia Gravis: A Sub-Analysis of the Phase 3 CHAMPION MG Study According to Chronic ivig Use at Study Entry (P1-5.013). Neurology. 2023;100(2).

Habib AA, Benatar M, Vu T, et al. Ravulizumab for the Treatment of Generalized Myasthenia Gravis: Timing of Response. MGFA Scientific Session (AANEM). 2023.

Juel V, Vu T; Casasnovas C, et al. Consistent Efficacy of Ravulizumab across Sex and Age Subgroups of Generalized Myasthenia Gravis patients: A Post Hoc Analysis of the CHAMPION MG study. Muscle & Nerve. 2022.

Mantegazza R, Meisel A, Annane D, et al. Ravulizumab Reduces Clinical Deteriorations in Patients with Generalised Myasthenia Gravis. European Journal of Neurology. 2022;29(1):61.

Meisel A, Annane D, Vu T, et al. Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open-label extension. Journal of Neurology. 2023;270:3862-3875.

Mozaffar T, Mantegazza R, Attarian S, et al. Ravulizumab in Adults with Generalized Myasthenia Gravis: A Post-Hoc Analysis of the Phase 3 CHAMPION MG Study by Muscle Domain. Musclar Distrophy Association. 2023.

Muppidi S, Narayanaswami P, Meisel A, et al. Achievement of Improved Post-Intervention Status in Patients with Generalized Myasthenia Gravis Treated with Ravulizumab during the CHAMPION MG Study (S5.008). 2023;100(2).

Vissing J, Mozaffar T, Mantegazza R, et al. Ravulizumab in Adults with Generalized Myasthenia Gravis: Post-Hoc Analysis of MG-ADL Item Score Change in CHAMPION MG. European Journal of Neurology. 2023;30(1):211.

Vu T, Meisel A, Mantegazza R, et al. Summary of Research: Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis. NEJM Evidence. 2023;12(5):1435-1438.

Vu T, Ortiz S, Katsuno M, et al. Ravulizumab pharmacokinetics and pharmacodynamics in patients with generalized myasthenia gravis. Journal of Neurology. 2023;270L3129-3137.

Study Period:

Date first participant randomized: 26 Mar 2019

Last participant last visit: 25 May 2023

Rationale:

Ravulizumab (ALXN1210) was engineered from eculizumab (h5G1.1 mAb), humanized monoclonal antibody that specifically binds with high affinity to the human terminal C5, inhibiting C5 enzymatic cleavage and thereby preventing the generation of the proinflammatory/prothrombotic complement activation products, C5a, and the cytolytic and proinflammatory/prothrombotic membrane attack complex, C5b-9, which are responsible for the antibody-mediated destruction of the NMJ, loss of AChR, and failure of neuromuscular transmission associated with gMG.

Ravulizumab preserves immediate and complete C5 inhibition while providing sustained complement inhibition throughout a prolonged dosing interval; it was specifically designed (and has subsequently been proven) to have an increased half-life relative to eculizumab. Therefore, ravulizumab requires less frequent (q8w) infusions relative to eculizumab (q2w infusions). Given that gMG is a chronic disease with a significant treatment burden, the relative convenience of the ravulizumab dosing regimen may increase participant satisfaction, increase treatment adherence, and ultimately, lead to improved health outcomes.

Ravulizumab offers a convenient dosing and immediate onset of action with effective and complete terminal complement inhibition at the end of the first infusion. Additionally, the dose regimen of ravulizumab has been optimized to reduce the exposure differences across the adult body-weight range by utilizing a weight-based dosing paradigm that provides immediate, complete, and sustained C5 inhibition over the entire dosing interval.

Objectives, Endpoints, and Statistical Methods

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the efficacy of ravulizumab compared with placebo in the treatment of generalized myasthenia gravis (gMG) based on the improvement in the Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile.	Change from Baseline in MG-ADL total score at Week 26 of the Randomized-Controlled Period.

Objectives	Endpoints
Secondary	
• To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in the Quantitative Myasthenia Gravis (QMG) total score.	• Change from Baseline in QMG total score at Week 26.
• To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on the improvement in quality of life measures.	• Change from Baseline in the Revised 15-Component Myasthenia Gravis Quality of Life (MG-QoL15r) score at Week 26. • Change from Baseline in Neuro-QoL Fatigue score at Week 26.
• To assess the efficacy of ravulizumab compared with placebo in the treatment of gMG based on other efficacy endpoints.	• Improvement of at least 3 points in the MG-ADL total score from Baseline at Week 26. • Improvement of at least 5 points in the QMG total score from Baseline at Week 26.
Exploratory	
• To assess the efficacy of ravulizumab in the treatment of gMG based on other efficacy endpoints throughout the study.	• Change from Baseline in the Myasthenia Gravis Composite (MGC) score at Week 26. • Myasthenia Gravis Foundation of America (MGFA) Post-Intervention Status (PIS) at Week 26. • Change from Baseline in Euro Quality of Life (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	
• To evaluate the PK/PD and immunogenicity of ravulizumab in the treatment of gMG throughout the study.	• Change in serum ravulizumab concentration over time. • Change in serum free C5 concentration over time. • Incidence of treatment-emergent antidrug antibodies over time.
Safety	
To characterize the overall safety of ravulizumab in the treatment of gMG.	• Incidence of adverse events and serious adverse events over time. • Changes from Baseline in vital signs and laboratory assessments.

Statistical Analyses:

Efficacy and safety summaries are presented as detailed in the following sections by treatment group (ie, RAV/RAV and PBO/RAV). For continuous variables, the change from Baseline was analyzed using MMRM. Summary statistics included the number of observations (n), mean, SD,

median, minimum, and maximum values. Frequencies and percentages were calculated for categorical variables.

Methodology:

This was a Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study to evaluate the safety and efficacy of ravulizumab for the treatment in participants with gMG. Eligible participants were stratified by region (North America, Europe, Asia-Pacific, and Japan) and randomized 1:1 to 1 of 2 treatment groups: (1) ravulizumab infusion or (2) placebo infusion. There were 3 periods in this study: Screening Period, RCP, and an OLE Period.

After the 26-Week RCP and assessments on Day 183 (Week 26), participants in the placebo group received a blinded loading dose of ravulizumab and participants in the ravulizumab group received a blinded ravulizumab dose of 900 mg. Starting Week 28, all participants began open-label ravulizumab maintenance doses q8w. For participants 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).

The OLE Period for each participant commenced when the participant received a dose of ravulizumab on Week 26 (Day 183) and was planned to continue for up to 4 years or until the product was registered or approved and available by prescription (in accordance with country-specific regulations), or the study drug can be provided via an Alexion post-trial access program (as allowed by local laws and regulations),whichever occurred first.

Throughout the study, rescue therapy (eg, high-dose corticosteroid, PP/PE, or IVIg) was allowed if a participant experienced clinical deterioration as defined in the study protocol.

Number of Participants (Planned and Analyzed):

Planned: 160 participants

Analyzed: 175 participants were randomized (Ravulizumab: 86 participants; Placebo: 89 participants); 161 were included in the Open-label Extension Set and 169 were included in the Ravulizumab Treated Set.

Diagnosis and Main Criteria for Inclusion and Exclusion:

This study enrolled male and female adult participants ≥ 18 years of age, inclusive, ≥ 40 kg body weight with confirmed MG Foundation of America Clinical Classification Class II to IV at Screening. Participants were allowed, but not required, to receive MG treatment at Screening; participants receiving azathioprine, ISTs, oral corticosteroids, or cholinesterase inhibitors prior to the Screening Visit must have remained on a stable dose for a specific time period as defined by the protocol. All participants must have been vaccinated against meningococcal infections prior to initiating study treatment. Participants of child-bearing potential and participants with partners of child-bearing potential were to follow protocol-specific contraception guidelines during study participation and 8 months after their last dose.

Participants were excluded from the study if they had active or untreated thymoma or history of thymic malignancy, an active infection, history of *N meningitidis* infection, HIV infection, had been recently hospitalized, were exhibiting an MG clinical deterioration, and if female participants were pregnant or breastfeeding. Prior therapies including IVIg, PE, and rituximab use were prohibited within the time frames specified in the protocol.

Study Intervention, Dose, and Mode of Administration:

Ravulizumab and placebo were supplied in 30 mL single use vials for IV infusion. Ravulizumab doses were weight-based, and given as a loading dose on Day 1, then maintenance doses on Days 15, 71, and 127 during the RCP. During the OLE Period, participants were given a blinded dose of ravulizumab at Day 183. All participants received open-label ravulizumab maintenance doses q8w starting on Day 197.

Supplemental ravulizumab (or placebo) dosing was required following PE/PP or IVIg rescue treatment on non-dosing days.

Duration of Study Intervention:

The study consisted of a 2- to 4-week Screening Period, a 26-Week RCP, and an OLE Period. The OLE Period for each participant was planned to continue for up to 4 years or until the product was registered or approved and available by prescription (in accordance with country-specific regulations), or the study drug can be provided via an Alexion post-trial access program (as allowed by local laws and regulations), whichever occurred first.

Summary of Results and Conclusions:

All participants who entered the OLE Period received administration of ravulizumab. Participants randomized to the ravulizumab group also received 26 weeks of ravulizumab treatment during the RCP (RAV/RAV treatment group). Participants randomized to receive placebo during the RCP had their first dose of ravulizumab at the start of the OLE Period (Day 183 Visit) (PBO/RAV treatment group).

Demographic and Other Baseline Characteristics:

Overall, 50.9% of participants in the Open-label Extension Set were female; 73.3% were White, and the mean age was 55.9 years at the time of first infusion of study drug (placebo or ravulizumab). A majority of participants (68.3%) were 18 to 65 years of age at the time of first infusion, and approximately half of the participants (55.3%) were in the baseline weight category ≥ 60 kg to < 100 kg. The population in the OLE Period was similar to that of the Primary Analysis Period.

Concomitant Medication:

In the OLE Period, physicians had the option to adjust IST therapies. A majority (68.3%) of participants had a change in concomitant MG medication during the OLE Period. The most common reason for change in corticosteroid therapies was improvement in MG symptoms. At the end of the OLE Period, 30.1% of patients decreased their daily dose of corticosteroid therapy and 12.4% of patients stopped corticosteroid therapy.

Exposure:

The mean duration of ravulizumab treatment (both during the RCP and OLE Period) was 851.6 days and the maximum exposure to ravulizumab treatment was 1332 days. The longer mean exposure in the RAV/RAV treatment group reflects the 26 weeks of ravulizumab received by participants during the RCP.

Efficacy Results:

MG-ADL and QMG total scores

- Treatment with ravulizumab resulted in rapid (as early as Week 1) and sustained improvements in MG-ADL total score and QMG total score from Baseline through the EOS in the RAV/RAV treatment group.
- During the OLE Period, rapid and sustained improvements in the MG-ADL total score and QMG total score were observed in the PBO/RAV treatment group which were of a similar magnitude as the improvements observed for the MG-ADL score and QMG total score in the RAV/RAV treatment group.

QMG ≥ 5-point Improvement

- 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 during the RCP. The proportion of clinical responders in the RAV/RAV treatment group remained consistent through the end of the OLE Period.
- During the OLE Period, the QMG ≥ 5-point response observed in the PBO/RAV treatment group was of a similar magnitude as the response observed in participants receiving ravulizumab for the duration of the study.

MG-QoL15r total score, Neuro-QoL fatigue score, and MG-ADL ≥ 3-point Improvement

- Although not statistically significant at Week 26, trends favoring ravulizumab were observed for the secondary endpoints of MGQoL15r total score, the Neuro-QoL fatigue score, and MG-ADL ≥ 3-point improvement which continued up through the EOS.

Safety Results:

- Overall during ravulizumab treatment:
  - AEs were experienced by 96.4% of participants and most common AEs ≥ 10% were COVID-19, headache, diarrhea, arthralgia, back pain, nausea, urinary tract infection, nasopharyngitis, fatigue, and dizziness.
  - Most AEs were Grade 1 (87%) or Grade 2 (66.3%) in severity.
  - Sixty-six (39.1%) participants had SAEs (154 events); the most frequent SAEs (≥ 2% of total participants) were COVID-19 (3.6%), MG (3.0%), and COVID-19 pneumonia (2.4%).
  - Three participants in the RAV/RAV treatment group had SAEs (unrelated to study drug) which led to discontinuation of study drug. None of the participants in the PBO/RAV treatment group discontinued study drug after switching to ravulizumab during the OLE Period.
  - Eight participants died during the study; 2 participants (ravulizumab) died during the RCP (cerebral hemorrhage and COVID-19 pneumonia), and 6 participants died during the OLE Period; 3 due to COVID-19, 1 due to drug toxicity to various

agents, 1 due to dehydration, and 1 due to an unknown reason. None of the deaths was considered to be related to the study drug.

- No cases of meningococcal infections were reported.
- Safety data are consistent with the known safety profile of ravulizumab with no new safety concerns.

Pharmacokinetic Results:

Mean ravulizumab serum concentration was measured during the RAV treatment period through the end of the OLE Period. Following initiation of the ravulizumab weight-based dosing regimen, therapeutic serum concentrations were overall achieved and maintained throughout the entire study period. Concentrations of ravulizumab were sustained at similar levels in PBO/RAV and RAV/RAV treated participants.

Pharmacodynamic Results:

Following initiation of weight-based ravulizumab dosing regimen, immediate and complete terminal complement inhibition (defined as serum free C5 < 0.5 µg/mL) was observed by the end of the first ravulizumab infusion and overall sustained throughout the entire study. Complete and sustained inhibition of serum free C5 (terminal complement) observed (free C5 serum concentrations of < 0.5 µg/mL) during the RCP in the RAV/RAV treatment group was overall maintained throughout the OLE Period. Likewise, for all participants in the PBO/RAV treatment group, complete inhibition of terminal complement free C5 was immediate following initiation of ravulizumab treatment at Week 26, and this complete inhibition was sustained overall under the prescribed maintenance dosing regimen.

Immunogenicity Results:

No treatment-emergent ADA positive responses were observed in participants in the RAV/RAV treatment group during the entire study. In the PBO/RAV treatment group, 2 of 82 (2.4%) participants showed treatment-emergent ADA positive responses at the early termination/EOS Visits during the OLE Period. Both treatment-emergent ADA positive responses were indeterminate, non-neutralizing with low titers and no apparent impact on efficacy, safety, PK, or PD was observed.

Conclusions:

- The treatment effect of ravulizumab was demonstrated as early as Week 1 and sustained through the EOS. After switching to ravulizumab treatment during the OLE Period, participants from the placebo group showed a rapid onset of efficacy of a similar magnitude of improvement in MG-ADL total score and QMG total score to that observed in the ravulizumab group during the RCP.
- Treatment with ravulizumab was well tolerated. No cases of meningococcal infections were reported.
- Treatment with ravulizumab provided continued complete and sustained inhibition of terminal complement (serum free C5) overall throughout the study.
- Two of 82 (2.4%) participants in the PBO/RAV treatment group showed treatment-emergent ADA positive responses at the early termination/EOS visits

during the OLE period. None of these participants exhibited anti-ravulizumab NAbs, and the presence of ADA had no apparent impact on efficacy, safety, PK, or PD.

- No new safety signals were identified, and the benefit-risk profile of ravulizumab for the treatment of adults with gMG remains favorable.