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ORIGINAL ARTICLE

Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis

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Abstract

BACKGROUND Generalized myasthenia gravis (gMG) is a rare, chronic, and debilitating autoimmune disease. Activation of the complement system by autoantibodies against the postsynaptic acetylcholine receptor (AChR) leads to destruction of the postsynaptic membrane and disruption of neuromuscular transmission. This trial evaluated ravulizumab, a long-acting inhibitor of terminal complement protein C5, as a treatment for gMG.

METHODS In this randomized, double-blind, placebo-controlled, multinational trial, we randomly assigned (1:1) patients with anti-AChR antibody-positive gMG to intravenous ravulizumab or placebo for 26 weeks. Patients received a loading dose on day 1, followed by maintenance doses on day 15 and every 8 weeks thereafter. The primary end point and first secondary end point (change from baseline to week 26 in patient-reported Myasthenia Gravis–Activities of Daily Living [MG-ADL] scale and clinician-reported Quantitative Myasthenia Gravis [QMG] total scores, respectively) were compared between the ravulizumab- and placebo-treated groups.

RESULTS In total, 175 patients were enrolled. Ravulizumab significantly increased the magnitude of mean changes from baseline to week 26 versus placebo in MG-ADL (−3.1 vs. −1.4; $P<0.001$) and QMG (−2.8 vs. −0.8; $P<0.001$) total scores. Improvements in both measures occurred within 1 week of ravulizumab initiation and were sustained through week 26. QMG total scores improved by 5 points or more in a significantly greater proportion of ravulizumab-treated patients than of those receiving placebo (30.0% vs. 11.3%; $P=0.005$). No notable differences in adverse events were observed.

CONCLUSIONS Ravulizumab demonstrated rapid and sustained improvements in both patient- and clinician-reported outcomes and had a side effect and adverse-event profile that did not limit treatment in adults with anti-AChR antibody-positive gMG. (Funded by Alexion, AstraZeneca Rare Disease; ClinicalTrials.gov number, NCT03920293; EudraCT number, 2018-003243-39.)

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**A list of the CHAMPION MG Study Group members is provided in the Supplementary Appendix, available at evidence.nejm.org.*

Introduction

Generalized myasthenia gravis (gMG) is a rare, chronic, and debilitating autoimmune disease resulting from impaired neuromuscular transmission.[1,2] It is characterized by fatigable muscle weakness, with significantly disabling clinical consequences including diplopia, ptosis, dysarthria, dysphagia, dyspnea, extreme fatigue, and impaired mobility.[1-4] The persistent functional impairment and burden of MG and its treatment have a major impact on patients' ability to perform activities of daily living (ADLs) and their quality of life.[5-10] Furthermore, inadequately controlled disease may predispose patients to clinical deterioration, including life-threatening myasthenic crises. The primary goal in the management of MG is therefore to maintain continuous control of disease activity and minimize associated symptoms.

Aberrant complement activation is a major effector mechanism of pathogenesis in patients with gMG.[3,11] The majority of patients with gMG (approximately 85%) have autoantibodies against the postsynaptic acetylcholine receptor (AChR).[12,13] Binding of anti-AChR antibodies leads to activation of the classical complement cascade, formation of the terminal complement complex (membrane attack complex), and consequent destruction of the postsynaptic membrane of the neuromuscular junction.[12,13]

Immunosuppressive therapies used to treat gMG suppress cellular mediators of the immune response, but most have a slow onset of action and do not directly target the complement system.[14,15] Furthermore, long-term treatment with glucocorticoids and other immunosuppressive therapies can be associated with serious side effects.[16,17] An effective, complement-targeted therapy that has a favorable dosing schedule, has an acceptable side-effect and adverse-event profile, and can consistently control continuous disease activity in gMG would be a valuable treatment option. Inhibition of terminal complement activation to prevent destruction of the neuromuscular junction in patients with anti-AChR antibody-positive gMG[18] has been shown to improve clinical outcomes with no treatment-limiting side effects in patients with refractory gMG.[19]

Ravulizumab is a humanized monoclonal antibody that specifically binds with high affinity to the human terminal complement protein C5, preventing disruption of neuromuscular transmission, presumably by inhibiting membrane attack complex-mediated destruction of the neuromuscular junction. Ravulizumab was engineered to maintain therapeutic serum concentrations over a long (8-week) dosing interval.[20] Evidence from phase 3 studies in paroxysmal nocturnal hemoglobinuria[21] and atypical hemolytic uremic syndrome[22] demonstrated that ravulizumab, administered at 8-week intervals, provides immediate and complete terminal C5 complement inhibition that is sustained throughout the dosing interval, with an acceptable side-effect and adverse-event profile. We therefore anticipated that ravulizumab, administered every 8 weeks, would provide sustained control of disease activity in gMG.

To evaluate the efficacy and safety of ravulizumab in adult patients with anti-AChR antibody-positive gMG, we conducted a phase 3, randomized, double-blind, placebo-controlled, multicenter trial (CHAMPION MG; ClinicalTrials.gov number, NCT03920293; EudraCT number, 2018-003243-39).

Methods

TRIAL DESIGN AND OVERSIGHT

After enrollment and a 2- to 4-week screening period, eligible patients were randomly assigned (1:1) at baseline (day 1) to receive either ravulizumab or placebo for 26 weeks. Patients were randomly assigned centrally using interactive response technology and randomization was stratified by region (North America, Europe, Asia-Pacific, and Japan). Following completion of the 26-week randomized, double-blind, placebo-controlled trial period (randomized trial period; the results of which are reported in this article), patients could enter an extension of the trial and receive open-label ravulizumab treatment for up to 4 years. The trial design is summarized in Figure S1 in the Supplementary Appendix.

The trial protocol was approved by the independent ethics committee or institutional review board at each participating institution. The trial was conducted in accordance with the provisions of the World Medical Association Declaration of Helsinki, the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice, and all applicable regulatory requirements. All patients provided written, informed consent.

Alexion Pharmaceuticals (now Alexion, AstraZeneca Rare Disease) designed the trial in consultation with the senior

and lead trial investigators, provided the investigational agents, oversaw the overall execution of the trial, managed and analyzed the data, vouches for the data and analysis, and made the decision to publish the data. Under the authors' guidance, the manuscript was drafted by Duncan Porter and Julie Ponting of Piper Medical Communications, funded by Alexion, AstraZeneca Rare Disease. Agreements concerning the confidentiality of the data were in place between the sponsor and the investigators/their institutions.

The trial was conducted during the Covid-19 pandemic; consequently, some trial activities were modified from the protocol, and mitigation strategies were implemented to ensure maintenance of treatment and patient safety while continuing the trial. Further details are included in the Supplementary Appendix (page 23 on Covid-19 mitigation strategies).

PATIENTS

Patients with anti-AChR antibody-positive MG, 18 years of age or older, and weighing 40 kg or more were eligible for the trial if they met the following criteria: a diagnosis of MG 6 months or more before screening; a Myasthenia Gravis Foundation of America clinical classification[23] of class II to IV at screening; a Myasthenia Gravis–Activities of Daily Living (MG-ADL) scale total score[24] of 6 or more at screening and randomization; and a positive serological test for anti-AChR antibodies at screening, as determined by a central laboratory using a ligand-binding assay. Patients were required to have been vaccinated against meningococcal infections within 3 years before initiating trial agent. Stable-dose immunosuppressive therapies (including oral glucocorticoids) or cholinesterase inhibitors were permitted throughout the randomized trial period.

Patients were excluded from the trial if they had active or untreated thymoma, a history of thymic carcinoma or thymic malignancy (unless deemed cured by adequate treatment with no evidence of recurrence for 5 years or more before screening), a history of thymectomy in the 12 months before screening, a history of *Neisseria meningitidis* infection, use of intravenous immunoglobulin or plasma exchange in the 4 weeks before randomization, use of rituximab in the 6 months before screening, or previous treatment with a complement inhibitor (e.g., eculizumab). Full details of the inclusion and exclusion criteria are provided in the Supplementary Appendix (page 18).

TRIAL PROCEDURES

Ravulizumab or matching placebo was administered intravenously. Ravulizumab dosing was based on the patient's body weight[21,22] (additional details are provided in the Supplementary Appendix, page 21). Patients received an initial loading dose of ravulizumab (2400, 2700, or 3000 mg) or placebo at baseline (day 1), followed by maintenance doses of ravulizumab (3000, 3300, or 3600 mg) or placebo on day 15 (week 2) and every 8 weeks thereafter.

Throughout the trial, additional clinic visits and/or rescue therapy (e.g., high-dose glucocorticoids, plasmapheresis/plasma exchange, or intravenous immunoglobulin) were allowed if a patient experienced symptom worsening or clinical deterioration (for the trial definition of clinical deterioration, see Supplementary Appendix, page 21).

Efficacy was assessed using the following validated outcome measures: the MG-ADL scale,[24] the Quantitative Myasthenia Gravis (QMG) score,[25] the revised 15-item Myasthenia Gravis Quality of Life (MG-QOL15r) questionnaire,[26] and the Neurological Quality of Life (Neuro-QoL) Fatigue subscale.[27] A copy of each measure is provided in the Supplementary Appendix (pages 24–28). The MG-ADL is an 8-item survey of patient-reported MG symptom severity, with each response graded from 0 (normal) to 3 (most severe)[24]; total MG-ADL scores range from 0 to 24. The minimal clinically important difference (MCID) on the MG-ADL scale is considered to be 2 points.[28] The QMG is a 13-item clinician-determined assessment of disease status in MG, with each item graded for severity from 0 (none) to 3 (severe); total scores range from 0 to 39.[25] The MCID on the QMG is reported to be 3 points.[29] The MG-QOL15r questionnaire (a revised version of the MG-QOL15[30]) is a 15-item health-related quality of life (HR-QoL) measure for MG, with each item having three response options: 0 (not at all), 1 (somewhat), and 2 (very much); total scores range from 0 to 30.[26] The Neuro-QoL Fatigue subscale is an instrument evaluating the effect of fatigue on the quality of life of patients with neurologic disorders.[27] It comprises 19 patient-reported items assessing the frequency of different aspects of fatigue over the past 7 days, answered using a 5-point scale ranging from 1 (never) to 5 (always); total scores range from 19 to 95. MCIDs have yet to be established for the MG-QOL15r questionnaire and the Neuro-QoL Fatigue subscale. For all four measures, a reduction in score denotes improvement in symptoms. MG-ADL and QMG were assessed at screening, baseline (day 1, predose), and weeks 1, 2, 4, 10,

12, 18, and 26. MG-QOL15r and Neuro-QoL Fatigue were assessed at baseline and weeks 4, 12, 18, and 26. Efficacy was also assessed based on the occurrence of clinical deterioration (as defined in the protocol; summarized in the Supplementary Appendix, page 21).

Safety and side effects were evaluated based on the frequency of adverse events (using the Medical Dictionary for Regulatory Activities version 24.0 Preferred Terms), clinical laboratory and vital sign findings, and electrocardiogram abnormalities.

END POINTS

The primary end point was change from baseline in MG-ADL total score at 26 weeks. Five hierarchical secondary end points were assessed at 26 weeks: change from baseline in QMG total score, responder analysis of the QMG total score (improvement from baseline of 5 points or more), change from baseline in MG-QOL15r score, change from baseline in Neuro-QoL Fatigue score, and responder analysis of the MG-ADL total score (improvement from baseline of 3 points or more). All end points were compared between ravulizumab and placebo. For the responder analyses of improvement in QMG and MG-ADL total scores, the predetermined end points were more conservative (greater improvement required) than the published MCIDs of 3 and 2 points, respectively (described earlier).

STATISTICAL ANALYSIS

Power calculations, based on the longitudinal change from baseline in MG-ADL total score observed previously,[19] indicated that 160 patients randomly assigned to ravulizumab and placebo in a 1:1 ratio were required to ensure 90% or greater power to reject the null hypothesis of no treatment effect, based on change from baseline in MG-ADL total score at week 26.

A mixed-effects model with repeated measures and the assumption that missing data were missing at random was used for the primary end point, using all available longitudinal data regardless of whether patients received rescue therapy. All randomly assigned individuals were included in the longitudinal models using the full analysis set. Missing data were not imputed; details of the numbers of patients missing specific outcomes are provided in Table S6 by treatment arm and trial visit. All continuous secondary end points related to change from baseline were analyzed similarly to the primary end point. The QMG and MG-ADL responder end points were analyzed using a generalized linear mixed model. A marginal model was applied in the analyses using the residual likelihood marginal expansion pseudo-likelihood technique.

A fixed-sequence hierarchical testing procedure was used to address multiplicity and to control the overall two-sided type I error of $\alpha = 0.05$, with the primary end point tested first, followed by the five secondary end points in the order described earlier. No inferences should be drawn from results after the failure of statistical significance in the hierarchy.

Several prespecified sensitivity analyses on the primary end point were performed, including placebo-based and delta-adjusted stress testing methods for handling missing data; excluding the randomization stratification from the model; including use of rescue therapy during the randomized trial period in the model; using the per-protocol analysis set; and using a modified full analysis set (excluding patients affected by the Covid-19 pandemic).

Further details of the statistical analysis are provided in the Supplementary Appendix (pages 21–22 on statistical models).

Results

PATIENTS

From March 2019 to November 2020, 175 patients were enrolled and randomly assigned to treatment at 85 centers in 13 countries: 86 patients (49%) received ravulizumab and 89 (51%) received placebo (Fig. 1). Baseline demographics and clinical characteristics were balanced (Table 1). Overall, 51% of patients were women, the mean age was 56 years, and most patients (54%) weighed 60 to 100 kg. The mean age at MG diagnosis was 46 years, and the mean time since diagnosis was 10 years (median, 6.5 years; range, 0.5–39.5 years). The trial population was slightly younger and had a lower proportion of Black or African American participants than would be expected in the patient population with MG in the United States (Table S1).

Baseline MG-ADL and QMG total scores indicated predominantly mild to moderate impairment of ADLs (median MG-ADL score, 9; range, 6–24) and mild to moderate disease severity (median QMG score, 15; range, 2–39).

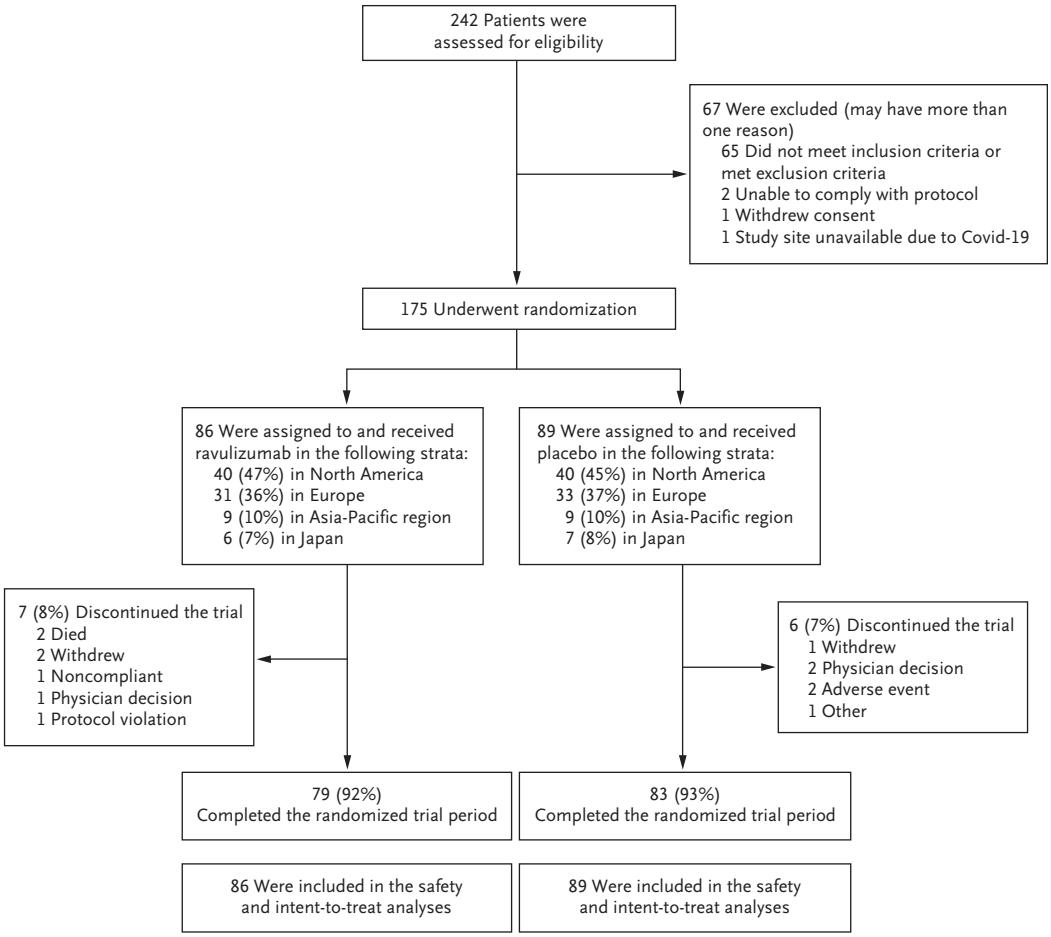

Figure 1. Enrollment, Randomization, and Follow-up of Patients.

Patients were stratified by region (North America, Europe, Asia-Pacific, and Japan). The full analysis set (intent-to-treat analysis) included all randomized patients with at least one dose of trial agent grouped by randomized treatment group. The safety set (safety analysis) included all patients with at least one dose of trial agent, grouped by treatment actually received.

The majority of patients (90%) were receiving immunosuppressive therapies at baseline; 47% were receiving two or more immunosuppressive therapies (Tables 1 and S2). Details of patients' use of immunosuppressant therapies in the 2 years before entering the trial are provided in Table S3. Further details of patients' prior history and management of MG are provided in Table S4.

Overall, 162 patients (93%) completed the 26 weeks of the trial (Fig. 1). The proportion of patients who discontinued was similar in the two groups.

EFFICACY-DETERMINED END POINT

The least-squares estimate of the mean MG-ADL change from baseline to week 26 was −3.1 (95% confidence interval [CI], −3.8 to −2.3) in the ravulizumab group and −1.4 (95% CI, −2.1 to −0.7) in the placebo group (P<0.001) (Fig. 2A and Table 2). A forest plot of mean MG-ADL change from baseline to week 26 by geographic region is provided in Figure S2; the point estimates for all regions were in favor of ravulizumab. The least-squares estimate of the mean QMG change was −2.8 (95% CI, −3.7 to −1.9) in the ravulizumab group and −0.8 (95% CI, −1.7 to 0.1) in the placebo group (P<0.001) (Fig. 2C and Table 2).

Improvements in MG-ADL and QMG scores with ravulizumab were observed within 1 week of treatment and were sustained through 26 weeks of treatment (Fig. 2A and 2C, respectively).

Prespecified sensitivity analyses on the primary outcome (Table S5) support the results of the primary analyses.

Table 1. Demographics and Clinical Characteristics of the Patients at Baseline.*			
Characteristic	**Ravulizumab (n=86)**	**Placebo (n=89)**	**All Patients (N=175)**
Female sex	44 (51)	45 (51)	89 (51)
Age at first trial dose, yr	58.0±13.8	53.3±16.1	55.6±15.1
Women	53.7±14.8	48.5±14.7	51.0±14.9
Men	62.6±11.2	58.3±16.1	60.4±14.0
Race†			
White	67 (78)	61 (69)	128 (73)
Asian	15 (17)	16 (18)	31 (18)
Black or African American	2 (2)	4 (4)	6 (3)
Other	0 (0)	3 (3)	3 (2)
Not reported	2 (2)	5 (6)	7 (4)
Body weight, kg	91.6±23.4	90.9±29.5	91.2±26.6
≥40 to <60	7 (8)	11 (12)	18 (10)
≥60 to <100	47 (55)	47 (53)	94 (54)
≥100	32 (37)	31 (35)	63 (36)
Age at MG diagnosis, yr	48.6±18.5	43.7±19.0	46.1±18.9
Time since gMG diagnosis, yr	9.8±9.7	10.0±8.9	9.9±9.3
Baseline MG-ADL score‡	9.1±2.6	8.9±2.3	9.0±2.5
Baseline QMG score§	14.8±5.2	14.5±5.3	14.7±5.2
Baseline MGFA classification¶			
IIa	22 (26)	24 (27)	46 (26)
IIb	17 (20)	15 (17)	32 (18)
IIIa	22 (26)	34 (38)	56 (32)
IIIb	19 (22)	11 (12)	30 (17)
IVa	2 (2)	4 (4)	6 (3)
IVb	4 (5)	1 (1)	5 (3)
Use of any immunosuppressive therapy at baseline	76 (88)	81 (91)	157 (90)
Glucocorticoids	56 (65)	65 (73)	121 (69)
Other immunosuppressive therapies‖	56 (65)	63 (71)	119 (68)
≥2 immunosuppressive therapies	36 (42)	47 (53)	83 (47)

* Data are presented as no. of patients (%) or means ±SD. gMG denotes generalized myasthenia gravis, MG myasthenia gravis, MG-ADL Myasthenia Gravis–Activities of Daily Living, MGFA Myasthenia Gravis Foundation of America, and QMG Quantitative Myasthenia Gravis.

† Self-reported by patients in response to an optional question in the case report form at the screening visit.

‡ Total scores on the MG-ADL scale range from 0 (normal) to 24 (most severe).

§ Total QMG scores range from 0 (none) to 39 (severe).

¶ The MGFA clinical classification categorizes MG into five classes according to the degree of muscle weakness. Classes II to IV rate the weakness of muscles other than ocular muscles as mild, moderate, or severe, subdivided into a (predominantly limb or axial muscles) and b (predominantly oropharyngeal or respiratory).

‖ Other immunosuppressive therapies included azathioprine, ciclosporin, methotrexate, mycophenolate mofetil, and tacrolimus.

A total of 27 of 76 patients (35.5%) in the ravulizumab group and 10 of 78 patients (12.8%) in the placebo group experienced an improvement of 5 points or more in their QMG score at week 26 (adjusted percentages: 30.0% [95% CI, 19.2 to 43.5] vs. 11.3% [95% CI, 5.6 to 21.5], respectively, P=0.0052; adjusted relative risk for ravulizumab/placebo: 2.7 [95% CI, 1.4 to 5.3]) (Fig. 2D and Table 2).

The additional secondary end points of change from baseline in MG-QOL15r score and Neuro-QoL Fatigue subscale score at 26 weeks did not meet statistical significance (the difference between the two groups in change in MG-QOL15r score was not statistically significant and as the end points were subject to hierarchical testing, significance is not reported for Neuro-QoL Fatigue) (Fig. 2E and 2F, respectively, and Table 2). A total

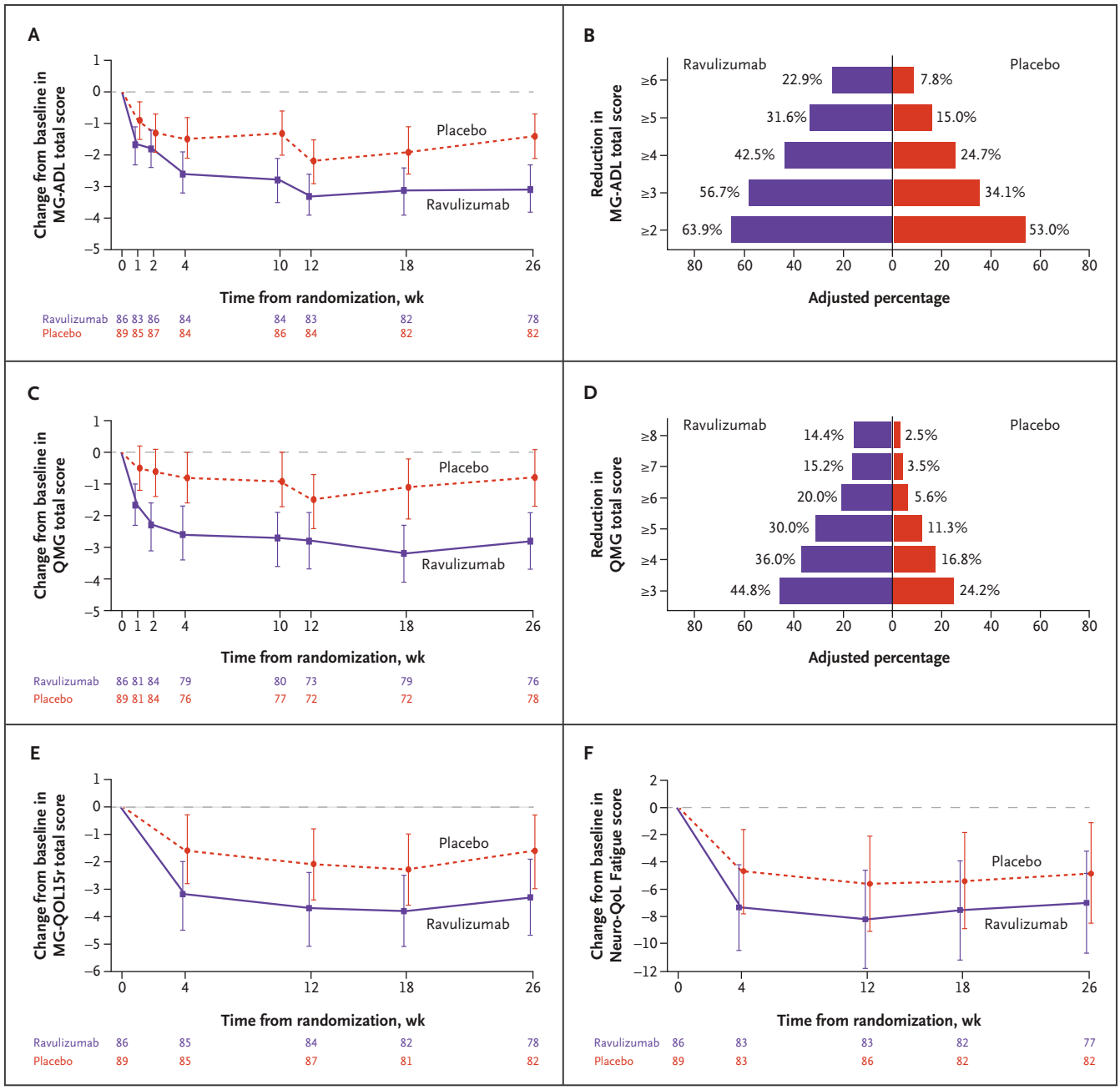

Figure 2. Trial Outcome Measures over Time, and Prespecified Responder Analyses at 26 Weeks.

Panel A shows changes from baseline in Myasthenia Gravis–Activities of Daily Living (MG-ADL) total score over time. Total scores on the MG-ADL scale range from 0 (normal) to 24 (most severe). Panel B shows minimum point improvements in MG-ADL total score at 26 weeks. Panel C shows changes from baseline in Quantitative Myasthenia Gravis (QMG) total score over time. Total QMG scores range from 0 (none) to 39 (severe). Panel D shows minimum point improvements in QMG total score at 26 weeks. Panel E shows changes from baseline in revised 15-item Myasthenia Gravis Quality of Life (MG-QOL15r) total score over time. Scores on the MG-QOL15r scale range from 0 (not at all affected) to 30 (very much affected). Panel F shows changes from baseline in Neurological Quality of Life (Neuro-QoL) Fatigue subscale score over time. Scores on the Neuro-QoL Fatigue scale range from 19 (never) to 95 (always). For all outcome measures, a reduction denotes improvement. Data shown in A, C, E, and F are least-squares means and 95% confidence intervals (CIs), using a mixed model for repeated measures; 95% CIs were not adjusted for multiplicity. Data shown in B and D are the proportions of patients with various point improvements in MG-ADL or QMG total scores at 26 weeks, using a generalized linear mixed model. The proportion of patients with a 5-point or greater improvement in QMG total score and the proportion with a 3-point or greater improvement in MG-ADL total score were prespecified secondary end points.

Table 2. Efficacy End Point Analyses.*				
End Point	Ravulizumab (n=86)	Placebo (n=89)	Treatment Effect (95% CI)	P Value
Primary				
Change from baseline in MG-ADL total score at 26 wk†	−3.1±0.38	−1.4±0.37	−1.6 (−2.6 to −0.7)	0.0009
Secondary‡				
Change from baseline in QMG total score at 26 wk§	−2.8±0.46	−0.8±0.45	−2.0 (−3.2 to −0.8)	0.0009
QMG ≥5-point improvement at 26 wk, %§	30.0	11.3	2.7 (1.4 to 5.3)¶	0.0052
Change from baseline in MG-QOL15r score at 26 wk‖	−3.3±0.71	−1.6±0.70	−1.7 (−3.4 to 0.1)	0.0636
Change from baseline in Neuro-QoL Fatigue score at 26 wk**	−7.0±1.92	−4.8±1.87	−2.2 (−6.9 to 2.6)	—††
MG-ADL ≥3-point improvement at 26 wk, %†	56.7	34.1	1.6 (1.2 to 2.3)¶	—††

* Changes from baseline at week 26 data are given as least-squares means ±SEM. Estimates are based on a mixed model for repeated measures analysis of variance that included treatment group, stratification factor region, and end point score at baseline, trial visit, and trial visit × treatment group interaction. Treatment effect is given as the difference of ravulizumab minus placebo with 95% confidence intervals (CIs) for the least-squares mean. Minimum points improvement data are given as adjusted percentage, with estimates based on a generalized linear mixed model that included treatment group, stratification factor region, and end point score at baseline, trial visit, and trial visit × treatment group interaction; treatment effect is given as adjusted relative risk with 95% CIs. MG-ADL denotes Myasthenia Gravis–Activities of Daily Living, MGFA Myasthenia Gravis Foundation of America, MG-QOL15r revised 15-item Myasthenia Gravis Quality of Life, Neuro-QoL Neurological Quality of Life, and QMG Quantitative Myasthenia Gravis.

† Total scores on the MG-ADL scale range from 0 (normal) to 24 (most severe); a reduction in score is an improvement.

‡ End points subject to hierarchical testing.

§ Total QMG scores range from 0 (none) to 39 (severe); a reduction in score is an improvement.

¶ Adjusted relative risk.

‖ Scores on the MG-QOL15r scale range from 0 (not at all affected) to 30 (very much affected); a reduction in score is an improvement.

** Scores on the Neuro-QoL Fatigue scale range from 19 (never) to 95 (always); a reduction in score is an improvement.

†† P value not reported as the secondary end points were subject to hierarchical testing and the previous end point was not statistically significant.

of 47 of 78 patients (60.3%) in the ravulizumab group and 30 of 82 patients (36.6%) in the placebo group achieved an improvement of 3 points or more in MG-ADL total score from baseline at week 26 (adjusted percentages: 56.7% [95% CI, 44.3 to 68.3] vs. 34.1% [95% CI, 23.8 to 46.1], respectively. To note, statistical significance is not reported because previous end points in the hierarchy were not statistically significant (adjusted relative risk for ravulizumab/placebo: 1.6 [95% CI, 1.2 to 2.3]) (Fig. 2B and Table 2).

The number of patients evaluated at each visit for the different end points is available under each panel in Figure 2. Table S6 provides the number (percentage) of patients missing specific outcomes, by treatment arm and trial visit.

Ten events in 8 patients (9%) in the ravulizumab group and 26 events in 15 patients (17%) in the placebo group met one or more of the criteria for clinical deterioration. Eight patients (9%) in the ravulizumab group and 14 (16%) in the placebo group received rescue therapy for 10 and 24 clinical deterioration events, respectively. Further details are provided in Table S7.

SAFETY

The proportions of patients who experienced adverse events, or adverse events that were considered by the investigator to be related to trial agent, were similar between the ravulizumab and placebo groups (Tables 3, S8, and S9). There were no notable differences in the types of adverse events between the two groups. The most frequent adverse event was headache, experienced by 16 patients (19%) in the ravulizumab group and 23 (26%) in the placebo group.

Serious adverse events were reported for 20 patients (23%) in the ravulizumab group and 14 (16%) in the placebo group (Table 3). The most frequent serious adverse events were related to worsening of MG (one patient receiving ravulizumab and three receiving placebo) and Covid-19 (two receiving ravulizumab and one receiving placebo). Two serious adverse events (dysphagia and tendonitis) in two patients in the ravulizumab group and four (cellulitis [two cases], herpes zoster infection, and infusion-related reaction) in four patients in the placebo group were categorized by the investigators as being related to the trial agent (Table S10). There were no cases of meningococcal

Table 3. Adverse Events.

Adverse Event*	Ravulizumab (n=86)		Placebo (n=89)	
	No. of Events	No. of Patients (%)	No. of Events	No. of Patients (%)
Any adverse event	350	78 (91)	341	77 (87)
Related to trial agent, as determined by investigator	56	29 (34)	61	30 (34)
Any adverse event, by severity grade†				
1	223	65 (76)	250	66 (74)
2	85	39 (45)	70	30 (34)
3	36	19 (22)	20	14 (16)
4	4	4 (5)	1	1 (1)
5	2	2 (2)	0	0
Any serious adverse event	35	20 (23)	16	14 (16)
Myasthenia gravis crisis	1	1 (1)	0	0
Myasthenia gravis‡	0	0	3	3 (3)
Related to trial agent, as determined by investigator§	2	2 (2)	4	4 (4)
Death	2¶	2 (2)	0	0
Adverse event leading to discontinuation of agent		2 (2)		3 (3)
Adverse event reported in ≥10% of patients in either group‖				
Headache	19	16 (19)	27	23 (26)
Diarrhea	14	13 (15)	15	11 (12)
Nausea	13	9 (10)	10	9 (10)

* Medical Dictionary for Regulatory Activities version 24.0 Preferred Term; patients with multiple events for a particular Preferred Term were counted only once for that term.

† Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03; details of adverse events reported as grade 3 to 5 are provided in Table S9.

‡ Worsening of myasthenia gravis.

§ Details are provided in Table S10.

¶ Neither death was considered related to the trial agent by the investigator; one death was due to Covid-19 and one was due to cerebral hemorrhage.

‖ Details of adverse events reported in 5% or more of patients in either group are provided in Table S8.

infection. There were two deaths in the ravulizumab group: one due to Covid-19 and one attributable to cerebral hemorrhage.

Discussion

In this study, the primary end point (change from baseline in MG-ADL total score at 26 weeks) and the principal secondary end point (change from baseline in QMG score at 26 weeks) were both statistically significantly improved with ravulizumab compared with placebo. A treatment effect, including improvement in clinical and functional outcomes, was observed within the first week of treatment and sustained throughout the 26-week randomized trial period. In the prespecified QMG responder analysis, approximately three times as many patients receiving ravulizumab experienced an improvement of 5 points or more in their QMG score compared with those receiving placebo.

The difference between ravulizumab and placebo was statistically significant for the primary and key secondary end points, despite a notable placebo effect. This was not unexpected; previous phase 2 and 3 clinical studies in gMG have reported similar placebo effects.[19,31-34] The underlying cause of the placebo effect is unclear; however, participation in a clinical trial, with more frequent and prolonged contact with clinical staff and enhanced compliance as a result of organized visits, may result in improved outcomes.[35-37]

The rapid onset of action and long dosing interval differentiate ravulizumab from immunosuppressive therapies.[38] For patients, the rapid onset of improvement in MG-ADL score reflects the ability to quickly regain function in routine activities. Ravulizumab's sustained efficacy, including beneficial effects on the incidence of clinical deterioration and use of rescue therapy, potentially reduces the burden of disease. The ravulizumab dosage administered in this trial (and approved in other clinical conditions) achieves

immediate, complete, and sustained C5 inhibition over the entire dosing interval,[39] and the weight-based dose regimen is optimized to reduce exposure differences across the adult body-weight range. Sustained clinical improvement achieved by consistent and predictable dosing (every 8 weeks) helps to address the unpredictability of a chronic, fluctuating disease and the significant ongoing treatment burden.

HR-QoL end points (changes in MG-QOL15r score and Neuro-QoL Fatigue subscale score) did not reach statistical significance. It is of interest to note that deterioration of HR-QoL in patients with MG during the Covid-19 pandemic has been reported.[40,41] This may have been a confounding factor in this trial and could have masked the true impact of treatment on HR-QoL. As shown in Table S11, when patients in the trial who had experienced a significant impact due to Covid-19 (e.g., those who had a Covid-19–related adverse event, terminated the trial early due to Covid-19, or were treated for Covid-19 with medications also used for MG) were excluded from the analysis (six patients from the ravulizumab group and four from the placebo group), there was a significant difference between ravulizumab and placebo in terms of improvement in MG-QOL15r score.

Ravulizumab did not have a treatment-limiting side effect profile in patients with gMG, with a safety profile consistent with that observed in phase 3 studies in paroxysmal nocturnal hemoglobinuria[21] and atypical hemolytic uremic syndrome[22] and in studies of the terminal complement inhibitor eculizumab.[19,42-44] No cases of meningococcal infection occurred during the randomized trial period, reflecting the effectiveness of risk-mitigation measures as reported for terminal complement inhibitor administration.[19,21,22]

One of the strengths of this phase 3 trial is the range of disease severity of the patients who were enrolled. The trial population included patients with mild to severe symptoms, those who were not receiving immunosuppressive therapies at baseline, and those who had been diagnosed as recently as 6 months before screening. Although the trial population may be slightly younger than the overall population with gMG (see representativeness information in Table S1), the trial outcomes are likely to be generalizable to the wider disease population, since the trial participants were drawn from races and ethnicities from a wide geography and reflected the relevant age range and spectrum of clinical characteristics of patients with gMG. The trial end points are also highly relevant outcome parameters for the clinical care of patients in the real world, as both patient- and clinician-reported assessments were used.[45,46]

Trial limitations include the influence of the Covid-19 pandemic. Although mitigation measures allowed the trial to continue collecting data per trial design, it is undetermined how the pandemic may have affected assessments, particularly those related to HR-QoL.

Conclusions

Ravulizumab provided rapid, efficacious treatment of adult patients with anti-AChR antibody-positive gMG with an acceptable side-effect and adverse-event profile, as determined by both patient- and clinician-rated outcomes. The results from this trial — the second phase 3 trial to report the effects of terminal complement inhibition in gMG — confirm the critical role played by complement in the pathogenesis of gMG and demonstrate that ravulizumab, with a mechanism of action designed to reduce the consequences of aberrant complement activation, can provide early and sustained treatment of anti-AChR antibody-positive gMG, without the burdensome side effects often observed with other treatments.

Disclosures

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