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ORIGINAL COMMUNICATION

'Minimal symptom expression' in patients with acetylcholine receptor antibody-positive refractory generalized myasthenia gravis treated with eculizumab

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Abstract

Background The efficacy and tolerability of eculizumab were assessed in REGAIN, a 26-week, phase 3, randomized, double-blind, placebo-controlled study in anti-acetylcholine receptor antibody-positive (AChR+) refractory generalized myasthenia gravis (gMG), and its open-label extension.

Methods Attainment of 'minimal symptom expression' was evaluated using patient-reported outcome measures of gMG symptoms [MG activities of daily living scale (MG-ADL), 15-item MG quality of life questionnaire (MG-QOL15)] at the completion of REGAIN and during the open-label extension. 'Minimal symptom expression' was defined as MG-ADL total score of 0–1 or MG-QOL15 total score of 0–3.

Results At REGAIN week 26, more eculizumab-treated patients achieved 'minimal symptom expression' versus placebo [MG-ADL: 21.4% vs 1.7%; difference 19.8%; 95% confidence interval (CI) 8.5, 31.0; $p=0.0007$; MG-QOL15: 16.1% vs 1.7%; difference 14.4%; 95% CI 4.3, 24.6; $p=0.0069$]. During the open-label extension, the proportion of patients in the placebo/eculizumab group who achieved 'minimal symptom expression' increased after initiating eculizumab treatment and was sustained through 130 weeks of open-label eculizumab (MG-ADL: 1.7 to 27.8%; MG-QOL15: 1.7 to 19.4%). At extension study week 130, similar proportions of patients in the eculizumab/eculizumab and placebo/eculizumab groups achieved 'minimal symptom expression' (MG-ADL: 22.9% and 27.8%, respectively, $p=0.7861$; MG-QOL15: 14.3% and 19.4%, respectively, $p=0.7531$). The long-term tolerability of eculizumab was consistent with previous reports.

Conclusions Patients with AChR+ refractory gMG who receive eculizumab can achieve sustained 'minimal symptom expression' based on patient-reported outcomes. 'Minimal symptom expression' may be a useful tool in measuring therapy effectiveness in gMG.

Trial registration ClinicalTrials.gov NCT01997229, NCT02301624.

Keywords Eculizumab · Refractory · Myasthenia gravis · Minimal symptom expression · Acetylcholine receptor

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Introduction

Generalized myasthenia gravis (gMG) is an autoimmune disorder characterized by muscle weakness that worsens with muscle use [1, 2]. Symptoms associated with gMG include muscle weakness resulting in dysarthria, dysphagia, dyspnoea and fatigue in the muscles of the face, neck, arms, hands and legs [3]. Although there is no generally recognized standard definition of 'refractory' disease in gMG, criteria for refractory disease that have been used include failure to respond to conventional treatments such as immunosuppressive therapies (ISTs), inability to reduce IST use without clinical relapse, intolerable adverse reactions to conventional treatments, requirement for large doses of potentially harmful agents such as ISTs, presence of comorbidities that contraindicate conventional treatments, requirement for repeated short-term rescue therapy (e.g. intravenous immunoglobulin and plasma exchange) and recurrent myasthenic crises [1, 4–7]. As a consequence of their continued disease symptoms and persistent morbidities, patients with refractory gMG experience a heavy clinical burden [4], which severely impairs their quality of life (QOL) [8].

More than 70% of patients with gMG produce autoantibodies directed against acetylcholine receptor (AChR); these patients are classed as being AChR+. The presence of these antibodies leads to reduced binding of the neurotransmitter acetylcholine to its receptor, accelerated degradation of AChRs and activation of the complement cascade [9–11]. Complement activation results in the cleavage of the terminal complement protein C5 into C5a and C5b by the C5 convertase enzyme complexes, thus activating the terminal complement cascade [12]. The combination of accelerated AChR degradation and the complement cascade results in structural damage to the neuromuscular junction, contributing to impaired neurotransmission and the muscle weakness characteristic of gMG [9].

The humanized monoclonal antibody eculizumab specifically binds to and inhibits cleavage of C5 [12]. The phase 3, randomized, placebo-controlled REGAIN study demonstrated the efficacy and tolerability of eculizumab in AChR+ refractory gMG during 6 months of therapy (NCT01997229) [13]. An interim analysis of the open-label extension of REGAIN found that eculizumab remained effective and well tolerated for up to 3 years of extended treatment (NCT02301624) [14]. During these studies, key efficacy endpoint assessments included the patient-reported MG activities of daily living scale (MG-ADL) [15] and the 15-item MG quality of life questionnaire (MG-QOL15) [16].

Current definitions of minimal symptoms in MG rely on physician evaluation. There are currently no definitions of minimal symptoms based exclusively on patients' assessments of their symptoms and QOL; this type of measurement could potentially be more meaningful for patients than physician-based evaluations. In a validation study for the MG-QOL15, patients in remission had a mean MG-QOL15 total score of 3.3 (standard deviation, 4.4), with a range of 0–15 [17]. Remission was defined as an MG composite score of 0 and a score of 0 on either the MG-ADL or the MG manual muscle test, with the exception that an eye closure score of 1 (mild weakness) was permitted [17].

For this analysis, we adapted this previous definition of remission [17] to develop the concept of 'minimal symptom expression', using the patient-reported measures of MG-ADL and MG-QOL15 that were used in REGAIN and the open-label extension study. This is the first analysis of its kind to use 'minimal symptom expression' as an efficacy endpoint in gMG.

Methods

Study design and participants

The efficacy and tolerability of eculizumab were assessed in a 6-month (26-week), phase 3, randomized, placebo-controlled study of patients with AChR+ refractory gMG aged 18 years or older (REGAIN) [13]. The first patient was enrolled on 30 April 2014. Eligible patients had confirmed AChR+ gMG; had an MG-ADL total score of at least 6; and had received at least two ISTs, or at least one IST with intravenous immunoglobulin or plasma exchange treatment at least four times in 12 months without symptom control. Exclusion criteria included ocular-only MG symptoms [Myasthenia Gravis Foundation of America (MGFA) class I] or myasthenic crisis at screening (MGFA class V). Full eligibility criteria have been published previously [13]. Patients could enrol in the open-label extension study in the 2 weeks after completing REGAIN to receive open-label eculizumab for up to a maximum of 4 years. The extension study was completed in January 2019 [14].

At least 2 weeks before starting study treatment, patients were vaccinated against *Neisseria meningitidis*. Patients who were not vaccinated at the appropriate time received prophylactic antibiotics until 2 weeks after vaccination. During the open-label extension study, when appropriate according to local guidelines, patients were revaccinated against *N. meningitidis*. During REGAIN, patients who previously received ISTs were required to maintain their pre-study dose and schedule. During the open-label extension of REGAIN, modifications to IST dose and schedule were permitted at the study investigator's discretion.

All patients provided written, informed consent. Independent ethics committees or institutional review boards

provided written approval for the study protocols and all amendments. The studies are registered at www.clinicaltrials.gov.

Study treatment dosing and scheduling

During REGAIN, patients randomized to eculizumab received an induction dose of 900 mg of eculizumab on day 1 and at weeks 1, 2 and 3, followed by a maintenance dose of 1200 mg of eculizumab at week 4 and every 2 weeks thereafter [13]. Placebo was administered using the same schedule. All patients who continued into the open-label extension study from REGAIN underwent a 4-week blinded induction phase. During this phase, patients who had received eculizumab during REGAIN received eculizumab 1200 mg on day 1 and at week 2, and placebo at weeks 1 and 3 (eculizumab/eculizumab group). Patients who had received placebo during REGAIN received eculizumab 900 mg on day 1 and at weeks 1, 2 and 3 (placebo/eculizumab group). All patients received open-label eculizumab 1200 mg at week 4 and every 2 weeks thereafter.

Assessments

The objective of REGAIN and the open-label extension study was to assess the tolerability of eculizumab and its efficacy, as measured by change in MG-ADL total score from each study's baseline. This sub-analysis evaluated the achievement of 'minimal symptom expression' in both studies, defined as achievement of an MG-ADL total score of 0–1 (range 0–24) or an MG-QOL15 total score of 0–3 (range 0–60).

The proportions of patients achieving 'minimal symptom expression' were calculated for the eculizumab and placebo treatment groups at week 26 of REGAIN and up to week 130 of the open-label extension (a total of 156 weeks of eculizumab treatment for the eculizumab/eculizumab group and 130 weeks of eculizumab treatment for the placebo/eculizumab group). Achievement of a clinically meaningful quantitative MG (QMG) response, defined as an improvement of at least 5 points in QMG total score, during the study was also recorded.

Adverse events were reported and coded by preferred term using the Medical Dictionary for Regulatory Activities version 20.1. MG exacerbations, rescue therapy use and discontinuations because of adverse events were also recorded.

Statistical analysis

The significance of differences between groups was evaluated by calculating *p* values based on Fisher's exact test for categorical variables and a two-sample *t*-test for continuous variables.

Results

Patient demographics and characteristics

Data are reported from the REGAIN study and its open-label extension for up to a maximum total of 156 weeks of eculizumab treatment. Of the 118 patients who completed REGAIN, 117 patients continued into the open-label study (eculizumab/eculizumab $n=56$, placebo/eculizumab $n=61$; Fig. 1) and were included in the efficacy and safety analyses. Patient demographics and characteristics were similar for the eculizumab/eculizumab and placebo/eculizumab groups, with the exception that there was a greater proportion of Asian patients in the placebo/eculizumab group (Table 1).

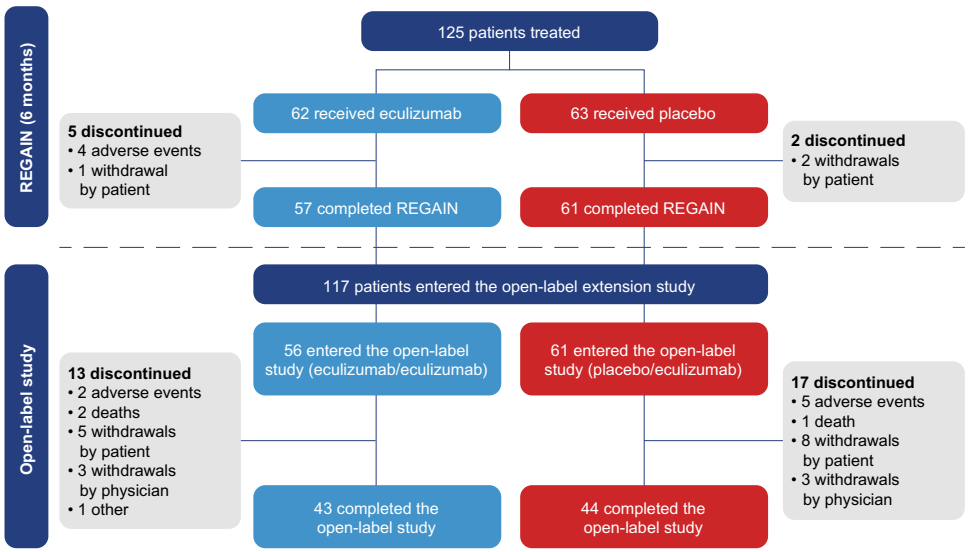

Fig. 1 Patient disposition in REGAIN and the open-label study

Table 1 Demographics and characteristics at REGAIN baseline of patients who continued from REGAIN into the open-label extension study

Variable	Eculizumab/eculizumab $n=56$	Placebo/eculizumab $n=61$	All patients $N=117$
Age, years[a], mean (SD)	46.8 (15.6)	47.0 (17.8)	46.9 (16.7)
Sex, *n* (%)			
Male	18 (32.1)	20 (32.8)	38 (32.5)
Female	38 (67.9)	41 (67.2)	79 (67.5)
Race, *n* (%)			
Asian	3 (5.4)	16 (26.2)	19 (16.2)
Black or African-American	0 (0.0)	2 (3.3)	2 (1.7)
White	47 (83.9)	41 (67.2)	88 (75.2)
Other/multiple/unknown	6 (10.7)	2 (3.3)	8 (6.8)
Duration of MG[b], years, mean (SD)	10.2 (7.9)	9.2 (8.6)	9.7 (8.2)
Baseline MG-ADL total score, mean (SD)	10.3 (3.0)	9.9 (2.6)	10.1 (2.8)
Baseline MG-QOL15 total score, mean (SD)	32.5 (12.0)	30.8 (12.9)	31.6 (12.5)

MG myasthenia gravis, *MG-ADL* myasthenia gravis activities of daily living questionnaire, *MG-QOL15* 15-item myasthenia gravis quality of life questionnaire, *SD* standard deviation

[a]At first dose in REGAIN

[b]Time from MG diagnosis to date of first dose in REGAIN

'Minimal symptom expression' status during REGAIN

At week 26 of REGAIN, a significantly higher proportion of patients receiving eculizumab achieved 'minimal symptom expression' than of those receiving placebo according to MG-ADL score (21.4% and 1.7%, respectively; difference 19.8%; 95% confidence interval [CI] 8.5, 31.0; $p=0.0007$; Fig. 2a) and MG-QOL15 score (16.1% and 1.7%, respectively; difference 14.4%; 95% CI 4.3, 24.6; $p=0.0069$; Fig. 2b).

'Minimal symptom expression' status during the open-label study

During the open-label extension, the proportion of patients in the eculizumab/eculizumab group with 'minimal symptom expression' was maintained for 2.5 years, between REGAIN week 26 and open-label week 130 (MG-ADL: 21.4% and 22.9%, respectively; MG-QOL15: 16.1% and 14.3%, respectively). In the placebo/eculizumab group, the proportion of patients with 'minimal symptom expression' increased to levels similar to those in the eculizumab/eculizumab group in the 4 weeks after starting open-label eculizumab therapy, between REGAIN week 26 and open-label week 4 (MG-ADL: 1.7% and 21.3%, respectively; MG-QOL15: 1.7% and 17.2%, respectively). This increase was sustained to open-label week 130 (MG-ADL: 27.8%; MG-QOL15: 19.4%).

At week 130 of the open-label extension, 'minimal symptom expression' was achieved by similar proportions of patients in the eculizumab/eculizumab and placebo/eculizumab groups as assessed by MG-ADL score (22.9% and 27.8%, respectively; difference −4.9%; 95% CI −25.1, 15.3; $p=0.7861$; Fig. 2a). The proportions of patients achieving 'minimal symptom expression' at week 130 based on MG-QOL15 score were also similar in the two groups, being 14.3% in the eculizumab/eculizumab group and 19.4% in the placebo/eculizumab group (difference −5.2%; 95% CI −22.5, 12.2; $p=0.7531$; Fig. 2b). Overall, 25.4% of eculizumab-treated patients experienced 'minimal symptom expression' according to MG-ADL and 16.9% according to MG-QOL15 at this time point.

Most eculizumab-treated patients who achieved 'minimal symptom expression' at any time also experienced a clinically meaningful improvement in physician-reported QMG total score, defined as an improvement of at least 5 points from eculizumab start. For 'minimal symptom expression' according to MG-ADL total score, this proportion was 85.7% (42/49) and, for 'minimal symptom expression' according to MG-QOL15 total score, it was 81.1% (30/37).

There was no significant difference in mean age at first eculizumab dose between eculizumab-treated patients who achieved 'minimal symptom expression' according to MG-ADL at any time during REGAIN and the open-label study (up to week 130) and those who did not (47.4 vs 47.0 years; $p=0.8847$). Mean disease duration at first eculizumab dose was shorter for patients who achieved 'minimal symptom expression' according to MG-ADL by open-label week 130 than for those who did not [8.27 (range 1.6–27.0) vs 11.16 (range 1.7–34.4) years; $p=0.0474$]. For achievement of 'minimal symptom expression' according to MG-QOL15 up to open-label week 130, there were no significant differences in mean age (44.6 vs 48.4 years; $p=0.2611$) or mean disease

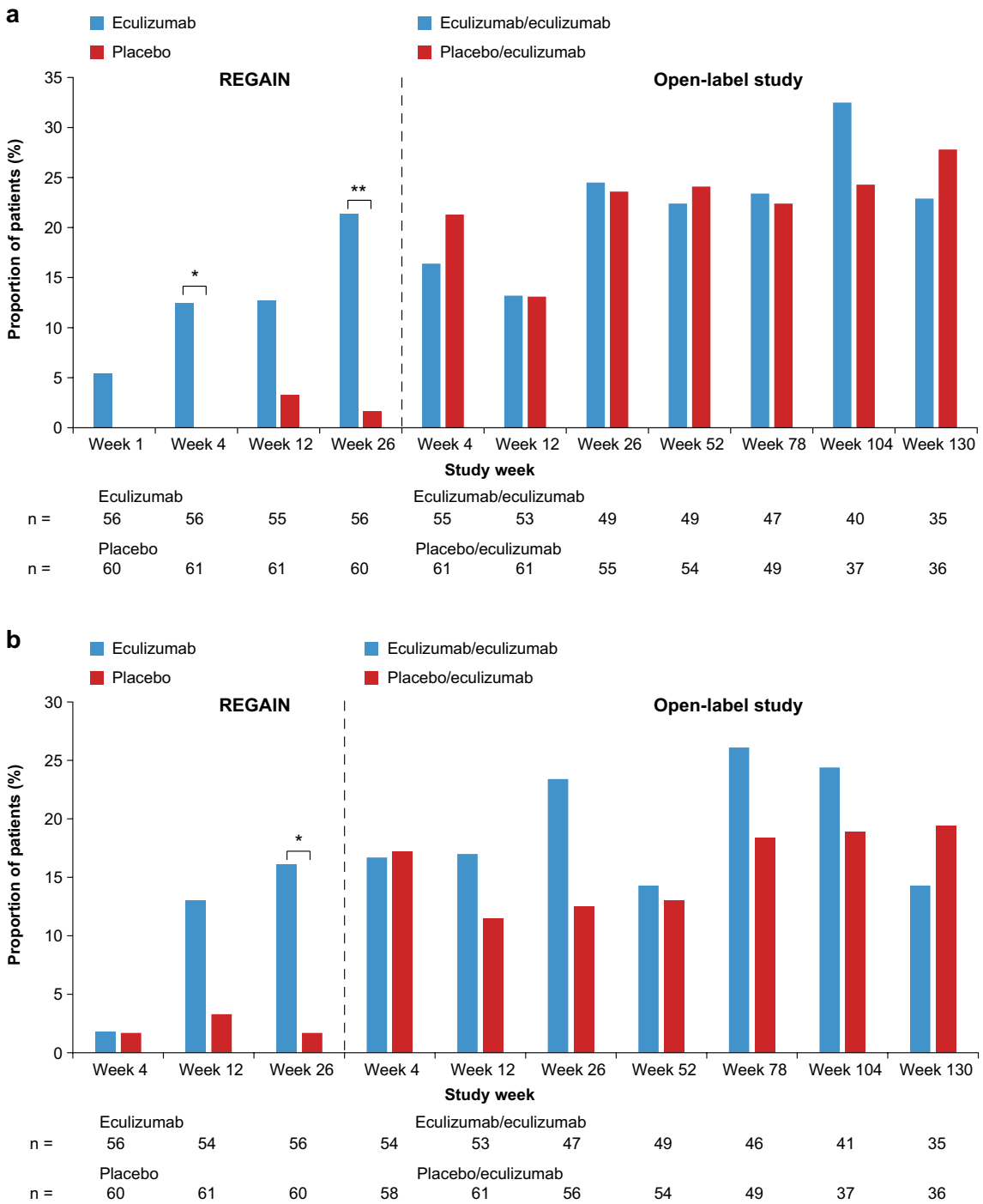

Fig. 2 **a** Proportions of patients achieving 'minimal symptom expression', defined as an MG-ADL total score of 0–1. **b** Proportions of patients achieving 'minimal symptom expression', defined as an MG-QOL15 total score of 0–3. *$p < 0.01$; **$p < 0.001$ vs placebo. p values are based on Fisher's exact test. *MG-ADL* myasthenia gravis activities of daily living questionnaire, *MG-QOL15* 15-item myasthenia gravis quality of life questionnaire

duration at first eculizumab dose [8.73 (range 1.6–24.6) vs 10.51 (range 1.7–34.4) years; $p = 0.2091$]. No significant differences were found between patients who did and did not achieve 'minimal symptom expression', according to either MG-ADL or MG-QOL15 scores, in other baseline characteristics, including sex, race, MGFA class, history of MG crisis and history of IST use. The only significant differences in baseline MG-ADL, MG-QOL15 and QMG

total scores were for MG-ADL ($p = 0.0380$) and MG-QOL15 ($p = 0.0487$) between patients who did achieve 'minimal symptom expression' according to MG-QOL15 and those who did not (Table 2).

The mean MG-ADL total score for the open-label study population decreased from 10.1 [standard deviation (SD) 2.80; $n = 117$] at REGAIN baseline to 3.9 (SD 3.08; $n = 71$) at open-label week 130. The mean MG-QOL15 total score also reduced between these time points, from 31.6 (SD 12.48) to 15.3 (SD 12.15).

Safety

Safety data have previously been published for REGAIN and an interim analysis of the open-label extension study [13, 14]. During these two studies, headache and nasopharyngitis were the most common adverse events among patients receiving eculizumab (experienced by 44.4% and 38.5%, respectively, from REGAIN baseline to week 130 of the open-label extension). MG worsening was experienced by 15.4% of eculizumab-treated patients, MG crisis by 3.4%

Table 2 Baseline demographics and characteristics of patients who did or did not achieve 'minimal symptom expression' at any time during REGAIN and the open-label extension study

Variable	MG-ADL total score 0–1			MG-QOL15 total score 0–3		
	Did achieve $n = 49$	Did not achieve $n = 68$	p value[a]	Did achieve $n = 37$	Did not achieve $n = 80$	p value[a]
Sex, *n* (%)						
Male	14 (28.6)	24 (35.3)	0.5491	11 (29.7)	27 (33.8)	0.8322
Female	35 (71.4)	44 (64.7)		26 (70.3)	53 (66.3)	
Race, *n* (%)						
Asian	7 (14.3)	12 (17.6)	0.5767	5 (13.5)	14 (17.5)	0.3377
Black or African American	1 (2.0)	1 (1.5)		1 (2.7)	1 (1.3)	
White	39 (79.6)	49 (72.1)		28 (75.7)	60 (75.0)	
Other/multiple/unknown	2 (4.1)	6 (8.8)		3 (8.1)	5 (6.3)	
Age at first eculizumab dose, years, mean (SD)	47.4 (18.79)	47.0 (15.25)	0.8847	44.6 (19.23)	48.4 (15.45)	0.2611
Duration of MG at first eculizumab dose[b], years, mean (SD)	8.3 (6.57)	11.2 (9.08)	0.0474	8.7 (5.97)	10.5 (9.05)	0.2091
MG-ADL total score at REGAIN baseline, mean (SD)	9.6 (3.08)	10.4 (2.55)	0.1061	9.3 (2.79)	10.5 (2.75)	0.0380
MG-QOL15 total score at REGAIN baseline, mean (SD)	31.0 (13.23)	32.0 (12.00)	0.6709	28.2 (14.14)	33.1 (11.40)	0.0487
QMG total score at REGAIN baseline, mean (SD)	16.8 (5.51)	17.1 (5.21)	0.8247	17.1 (5.77)	16.9 (5.13)	0.9034
Patients with MGFA class at REGAIN screening, *n* (%)						
IIa	10 (20.4)	14 (20.6)	0.7087	10 (27.0)	14 (17.5)	0.7954
IIb	11 (22.4)	8 (11.8)		7 (18.9)	12 (15.0)	
IIIa	13 (26.5)	21 (30.9)		10 (27.0)	24 (30.0)	
IIIb	10 (20.4)	18 (26.5)		8 (21.6)	20 (25.0)	
IVa	2 (4.1)	4 (5.9)		1 (2.7)	5 (6.3)	
IVb	3 (6.1)	3 (4.4)		1 (2.7)	5 (6.3)	
Patients with history of MG crisis before REGAIN, *n* (%)	8 (16.3)	13 (19.1)	0.8091	6 (16.2)	15 (18.8)	0.8018
Patients using ISTs before REGAIN, *n* (%)						
1 IST	0 (0.0)	2 (2.9)	0.1818	0 (0.0)	2 (2.5)	0.0520
2 ISTs	27 (55.1)	26 (38.2)		22 (59.5)	31 (38.8)	
3 ISTs	15 (30.6)	23 (33.8)		12 (32.4)	26 (32.5)	
≥ 4 ISTs	7 (14.3)	17 (25.0)		3 (8.1)	21 (26.3)	

IST immunosuppressive therapy, *MG* myasthenia gravis, *MG-ADL* myasthenia gravis activities of daily living scale, *MGFA* Myasthenia Gravis Foundation of America, *MG-QOL15* 15-item myasthenia gravis quality of life questionnaire, *QMG* quantitative myasthenia gravis scale, *SD* standard deviation

[a]The significance of differences between groups was evaluated by calculating p values based on Fisher's exact test for categorical variables and a two-sample t-test for continuous variables

[b]Time from MG diagnosis to date of first eculizumab dose

and MG exacerbations by 29.1%. A total of 11 patients discontinued eculizumab therapy owing to adverse events during the two studies. One patient contracted a meningococcal infection, which was resolved with antibiotic treatment [13]. Three deaths were reported in patients with important comorbidities that were likely to have contributed to the clinical outcome [13].

Discussion

This analysis found that, at the end of REGAIN, a significantly greater proportion of patients with AChR+ refractory gMG treated with eculizumab experienced 'minimal symptom expression' than of those receiving placebo according to an MG-ADL total score of 0–1 or an MG-QOL15 total score of 0–3. The proportions of patients experiencing 'minimal symptom expression' were maintained through 2.5 years of open-label eculizumab therapy in the extension study.

The only significant difference in baseline characteristics between patients who did and did not achieve 'minimal symptom expression' according to MG-ADL was in disease duration, and the only significant differences in the achievement of 'minimal symptom expression' according to MG-QOL15 were in MG-ADL and MG-QOL15 total scores at REGAIN baseline. The difference in baseline MG-ADL total score between these groups was small (1.2) and not clinically relevant. The baseline MG-QOL15 score was 4.9 points lower in patients who did achieve 'minimal symptom expression' according to MG-QOL15 than in those who did not, which may simply reflect that less improvement was required for patients with a lower baseline MG-QOL15 score to achieve a score of 3 or less. Overall, patients who did achieve 'minimal symptom expression' did not have less severe disease before eculizumab treatment than those who did not achieve it.

It is notable that, among a group of patients with refractory gMG with a mean MG-ADL total score of 10.1 at the start of REGAIN, approximately a quarter reported 'minimal symptom expression' defined as an MG-ADL total score of 0–1 through week 130 of the open-label study, by which time point the mean MG-ADL total score had reduced by more than half to 3.9. This reflects patient-reported improvements in disease burden in excess of the two-point reduction in MG-ADL total score that is considered to be a clinically meaningful improvement [18] to a level that has previously been described as disease remission [17]. In addition, 'minimal symptom expression', defined as an MG-QOL15 total score of 0–3, was achieved by one-sixth of these patients, and the mean MG-QOL15 total score halved between the start of REGAIN (31.6) and week 130 of the open-label study (15.3). The smaller proportion achieving 'minimal symptom expression' according to MG-QOL15 versus MG-ADL (one-sixth vs one-quarter) may be due to the conservative MG-QOL15 total score range (0–3) used in the definition of 'minimal symptom expression' in this analysis.

A correlation between changes in patient-reported MG-ADL scores and physician-assessed QMG scores has been described previously [19, 20]. In REGAIN and its open-label extension, patient-reported improvements were reflected in improvements in physician-reported outcomes assessed using QMG scoring. Almost half of eculizumab-treated patients achieved a clinically meaningful improvement in QMG total score (a reduction of at least 5 points) in the 26 weeks of REGAIN, and significant decreases in mean QMG total scores with eculizumab were maintained for up to 3 years during REGAIN and its open-label extension [13, 14]. In this analysis, most patients who achieved patient-reported 'minimal symptom expression' also achieved a clinically meaningful physician-reported QMG response.

The long-term tolerability of eculizumab was consistent with its known adverse event profile from established indications [21–25], and no new safety signals were observed since the interim analysis of the open-label extension study [14].

The main limitation of this *post hoc* analysis is the open-label design of the extension study, which could yield unconscious bias in reporting. Given that over 90% of patients who enrolled in REGAIN continued into the open-label study, selection bias in the open-label study population is unlikely. Further, the novel definition of 'minimal symptom expression' used in this analysis was derived from previous definitions of remission and has not yet been formally validated. In addition, further research is needed to evaluate the optimal range for this patient-reported assessment because this analysis used a conservative MG-QOL15 total score range of 0–3 to indicate 'minimal symptom expression'.

In conclusion, the results of this analysis confirm a rapid and sustained clinical response to eculizumab in patients with refractory gMG, reflected in the higher proportion reporting 'minimal symptom expression' with eculizumab than with placebo. Despite having refractory MG, individuals can achieve long-term 'minimal symptom expression' with eculizumab therapy. The current lack of validated definitions of minimal symptoms based exclusively on patients' assessments of their symptoms and QOL makes it difficult to comment on the generalizability of these findings. However, this type of assessment could potentially be more meaningful for patients than physician-based evaluations. 'Minimal symptom expression' based on quantitative, patient-reported outcomes may, therefore, be a useful tool in measuring patient progress following therapeutic intervention.

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Data availability Qualified academic investigators may request participant-level, de-identified clinical data and supporting documents (statistical analysis plan and protocol) pertaining to this study. Further details regarding data availability, instructions for requesting information and our data disclosure policy are available on the Alexion website (https://alexion.com/research-development).

Compliance with ethical standards

Conflicts of interest This work was funded by Alexion Pharmaceuticals. J.V. has received research and travel support, and/or speaker honoraria from Alexion Pharmaceuticals and Sanofi/Genzyme, and has served on advisory boards or as a consultant for Asklepios Biopharmaceuticals, Audentes Therapeutics, Novartis Pharma AG, PTC Therapeutics, Roche, Sanofi/Genzyme, Santhera Pharmaceuticals, Sarepta Therapeutics, and Stealth Biotherapeutics within the past 3 years. S.J. is a member of an international advisory board for Alexion Pharmaceuticals, has been an advisory board member for Alnylam Pharmaceuticals and Argenx BVBA, has received speaker fees from Terumo BCT, and has received research support from the Wellcome Trust Clinical Research Facility and Centre for Rare Diseases at the University Hospitals Birmingham, UK. K.P.F. was employed by and owns stock in Alexion Pharmaceuticals and is employed by Alnylam Pharmaceuticals. F.O'B. is employed by, and owns stock in, Alexion Pharmaceuticals. J.F.H. has received research support from Alexion Pharmaceuticals, argenx BVBA, the Centers for Disease Control and Prevention (Atlanta, GA, USA), the Muscular Dystrophy Association, the National Institutes of Health (including the National Institute of Neurological Disorders and Stroke and the National Institute of Arthritis and Musculoskeletal and Skin Diseases) and Ra Pharmaceuticals; has received honoraria from Alexion Pharmaceuticals; and has received non-financial support from Alexion Pharmaceuticals, argenx BVBA, Ra Pharmaceuticals and Toleranzia.

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