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A Phase 3 Multicenter, Prospective, Open-Label Efficacy and Safety Study of Immune Globulin (Human) 10% Caprylate/Chromatography Purified in Patients with Myasthenia Gravis Exacerbations

Guntis Karelis[a] Rodica Balasa[b] Jan L. De Bleecker[c] Tima Stuchevskaya[d] Andres Villa[e] Philip Van Damme[f] Emmeline Lagrange[g] Jeannine M. Heckmann[h] Michael Nicolle[i] Crisandra Vilciu[j] Vera Bril[k, l] Elsa Mondou[m] Rhonda Griffin[m] Junliang Chen[m] Waleska Henriquez[m] Beatriz Garcia[n] Sandra Camprubi[n] Jaume Ayguasanosa[n]

[a]Department of Infectology and Dermatology, Rīga Stradiņš University, Rīga, Latvia; [b]Spitalul Clinic Județean de Urgență Târgu Mureş, Clinica Neurologie I, Târgu Mureş, Romania; [c]Department of Neurology and Neuromuscular Reference Center, Ghent University Hospital, Ghent, Belgium; [d]City Hospital No. 2, Department of Neurology (Neuromuscular Center), Saint Petersburg, Russia; [e]Hospital General de Agudos Dr. J. M. Ramos Mejia Urquiza 609, CABA, Buenos Aires, Argentina; [f]Department of Neurology, University Hospitals Leuven, Department of Neurosciences, KU Leuven and Center for Brain and Disease Research, VIB, Leuven, Belgium; [g]Service de Neurologie, Centre Hospitalier Universitaire de Grenoble, Grenoble, France; [h]Division of Neurology, Department of Medicine, University of Cape Town, New Groote Schuur Hospital, Cape Town, South Africa; [i]Department of Clinical Neurological Sciences, Western University, London, ON, Canada; [j]Department of Neurology, Institutul Clinic Fundeni, Bucharest, Romania; [k]Ellen and Martin Prosserman Centre for Neuromuscular Diseases, Division of Neurology, Department of Medicine, University Health Network, University of Toronto, Toronto, ON, Canada; [l]Institute for Research and Medical Consultations, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; [m]Grifols Bioscience Research Group, Research Triangle Park, NC, USA; [n]Grifols Bioscience Research Group, Sant Cugat del Vallès, Spain

Keywords
Myasthenia gravis · Immune globulin caprylate/chromatography purified · IV immune globulin · Exacerbations

Abstract

Background: Myasthenia gravis (MG) is an autoimmune disorder affecting neuromuscular transmission. Exacerbations may involve increasing bulbar weakness and/or sudden respiratory failure, both of which can be critically disabling. Management of MG exacerbations includes plasma exchange and intravenous immunoglobulin (IVIG); they are equally effective, but patients experience fewer side effects with IVIG. The objective of this study was to assess the efficacy and safety of immune globulin caprylate/chromatography purified (IGIV-C) in subjects with MG exacerbations. ***Methods:*** This prospective, open-label, non-controlled 28-day clinical trial was conducted in adults with MG Foundation of America class IVb or V status. Subjects received IGIV-C 2 g/kg over 2 consecutive days (1 g/kg/day) and were assessed for efficacy/safety on Days 7, 14, 21, and 28. The pri-

E-Mail karger@karger.com
www.karger.com/ene

Guntis Karelis, MD, PhD
Department of Infectology and Dermatology
Rīga Stradiņš University
LV–1007 Rīga (Latvia)
E-Mail guntis.karelis@gmail.com

mary efficacy endpoint was the change from Baseline in quantitative MG (QMG) score to Day 14. Secondary endpoints of clinical response, Baseline to Day 14, included at least a 3-point decrease in QMG and MG Composite and a 2-point decrease in MG-activities of daily living (MG-ADL). ***Results:*** Forty-nine subjects enrolled. The change in QMG score at Day 14 was significant ($p < 0.001$) in the Evaluable (–6.4, $n = 43$) and Safety (–6.7, $n = 49$) populations. Among evaluable subjects, Day 14 response rates were 77, 86, and 88% for QMG, MG Composite, and MG-ADL, respectively. IGIV-C showed good tolerability with no serious adverse events. ***Conclusions:*** The results of this study show that IGIV-C was effective, safe, and well tolerated in the treatment of MG exacerbations.

Introduction

Myasthenia gravis (MG) is an autoimmune disease mediated by the presence of pathogenic antibodies against components of the postsynaptic striated muscle membrane of the neuromuscular junction. In most cases, the autoantibodies are against the acetylcholine receptor (AChR); other targets, such as muscle-specific kinase (MuSK) and lipoprotein-related protein 4, have also been described [1, 2]. MG is characterized by fluctuating muscle weakness that may be fatigable; it worsens with repetitive physical exertion and improves with rest. In 80–85% of patients, MG evolves from only ocular symptoms (ptosis and diplopia) at initial presentation to generalized MG with weakness affecting other muscle groups [1]. In some patients, substantial worsening of generalized weakness – especially if involving bulbar muscles, triggered by infection, surgery, stress, medication, or other factors – may lead to impending or manifest MG exacerbations. Acute episodes of MG exacerbations with respiratory muscle and severe swallowing disorders occur in 20–30% of patients [1, 2].

First-line treatment of patients with MG involves cholinesterase inhibitors augmented by corticosteroid (CS) therapy and other immunosuppressants and immunomodulators to control worsening generalized weakness [3]. Treatment of severe MG exacerbations with bulbar and/or respiratory involvement typically includes intravenous immune globulin (IVIG) and plasma exchange (PLEX). According to the International Consensus Guidance for management of MG [4], IVIG and PLEX are mainstays of management in myasthenic crisis, and the use of IVIG and PLEX in this setting is supported by a range of clinical studies [5–10]. A relatively rapid onset of action makes these agents useful for patients with worsening or life-threatening MG symptoms and, although they are equally effective, IVIG is associated with fewer side effects than PLEX [11, 12], and it can be used in patients with a history of non-response or contraindications to PLEX [13]. These clinical benefits provide the rationale for recommendations of the use of IVIG for acute exacerbations of MG in multiple guidelines, including the American Academy of Neurology, the European Federation of Neurological Societies, the American Academy of Allergy, Asthma and Immunology [14], and the Association of British Neurologists, among others [4, 15–17]. In most patients, IVIG is administered at doses of 2 g/kg of body weight over 2 to 5 days. Its exact mechanism of action of IVIG is unclear but may include blockade of Fc receptors on macrophages, reduced complement activation, and diminished production of antibodies and cytokines [18].

Immune Globulin (Human), 10% Caprylate/Chromatography Purified ([IGIV-C] Gamunex®-C, Grifols Inc., Clayton, NC, USA) is a sterile solution of human immune globulin (100 mg/mL) purified from human plasma intended for IV administration. In the European Union, IGIV-C received marketing authorization for primary humoral immunodeficiency, primary immune thrombocytopenia, secondary immune deficiencies, Guillain-Barré syndrome, and Kawasaki disease in 2006 and for chronic inflammatory demyelinating polyneuropathy in 2009; worldwide, IGIV-C is currently approved in 55 countries. Clinical trial and post-marketing experience have demonstrated that IGIV-C is safe and well-tolerated for licensed indications requiring a 2 g/kg dose. The objective of the present study was to evaluate the efficacy of an IV infusion of IGIV-C (2 g/kg administered over 2 consecutive days at a dose of 1 g/kg per day) in subjects with MG exacerbations.

Methods

The study protocol was approved by Institutional Review Boards/Independent Ethics Committees/Research Ethics Boards at all participating institutions (see Supporting Information for full listing) and by regulatory authorities. It was registered at ClinicalTrials.gov (NCT02413580) and European Clinical Trials Register (EudraCT number 2013-005098-28). All subjects provided written informed consent, and the investigators ensured that all study-related activities were conducted in full conformance with appropriate local laws, regulations, International Conference on Harmonisation Good Clinical Practice, and the Declaration of Helsinki.

Subjects

To be eligible, subjects had to be aged ≥18 years and have MG exacerbations not attributable to an infection or change in medication (defined as worsening of MG symptoms to MG Foundation of America (MGFA) class IVb or V) while on long-term (≥8 weeks) CS MG treatment. Subjects were excluded if they had received either IVIG or PLEX within 30 days, had modified CS dosage within the last 2 weeks, were known to be positive for antibodies against MuSK, or had MG exacerbations attributable to change in medication or infection (manifested by fever, positive blood culture, leukocytosis, pulmonary infiltrate on X-ray, and/or per investigator's judgment).

Study Design

This multicenter, prospective, open-label, non-controlled study assessing the efficacy and safety of IGIV-C in subjects with MG exacerbations was conducted at 15 enrolling centers in 10 countries (Latvia, Belgium, Czech Republic, Poland, Romania, Russian Federation, Argentina, France, South Africa, Canada). A single-dose course of IGIV-C was followed by 28 days of post-infusion assessments. The total duration of study participation for each subject was up to 28 ± 2 days.

Treatment

All subjects received an infusion of IGIV-C 2 g/kg body weight administered immediately after Baseline (Day 0) assessments were completed as a 1 g/kg/day dose over 2 consecutive days.

Assessments

Baseline assessments included Quantitative MG (QMG), MG Composite, MG-Activities of Daily Living (ADL), local laboratory testing (hematology, chemistry, hemolysis monitoring), and AChR and MuSK antibody testing. QMG, MG Composite, and MG-ADL were performed on Days 7, 14, 21, and 28. AChR antibody testing was done at Days 14 and 28, and hemolysis laboratory assessments were repeated between 8 and 24 h after the second day of IGIV-C infusion and also on Days 7 and 28 (i.e., direct antiglobulin testing [DAT], serum/plasma free hemoglobin, haptoglobin, lactate dehydrogenase, fractionated bilirubin, examination of blood smear for spherocytes, absolute reticulocyte count, and assessment for hemoglobinuria).

Changes to routine MG therapy (e.g., CS, cholinesterase inhibitors or other immunosuppressants) were not permitted until Day 14 after the primary efficacy assessment, unless necessary for safety reasons per the investigator's assessment. Additionally cholinesterase inhibitors were to be held 12 h prior to QMG assessment with the exception of the Baseline visit.

Outcomes

Efficacy

The primary efficacy outcome measure was changed in QMG score from Baseline to Day 14, similar to precedent studies [11, 15, 19–22]. The 3 secondary efficacy endpoints were percentage of subjects with a clinical improvement from Baseline to Day 14 defined as a categorical response: for QMG at least a 3-point decrease [23], for MG Composite at least a 3-point decrease [24], and for MG-ADL at least a 2-point decrease [25]. Exploratory efficacy endpoints included change from baseline in QMG, MG Composite, and MG-ADL at other time points relative to Baseline, and percentage of subjects with clinical improvement (thresholds defined above) in QMG, MG Composite, and MG-ADL at all other time points.

Safety

Safety outcomes included adverse events, suspected adverse drug reactions, adverse reactions, serious adverse events (AEs), vital signs, physical assessments, blood biochemistry and hematology, thromboembolic events risk, and hemolysis detection.

Statistical Analysis

Sample size calculations were derived from the study by Zinman et al. [19] indicating that the standard deviation (SD) for change from baseline to Day 14 in QMG score was in the range of 2.74–3.48. Considering the international scope of this study, an SD of 6.0 for QMG score change from baseline to Day 14 was assumed. Therefore, with a 2-sided test, 33 subjects were needed to have 90% power to detect a clinically significant improvement of 3.5 points in mean change in QMG [19]. Fifty subjects were planned to be enrolled in order to assure that a study population of 33 subjects would be evaluable for efficacy.

The Evaluable population consisted of subjects who received 2 g/kg IGIV-C over 2 consecutive days and had valid Baseline and Day 14 QMG assessments and no major/critical protocol deviations impacting primary efficacy analysis. The Safety population included all subjects who received any IGIV-C.

For the primary efficacy outcome, a paired *t* test (comparison pre- and post-) was used to test for treatment effect, and the 95% confidence interval (CI) was calculated. The hypothesis was to test the null hypothesis H_0 ($\mu_d = 0$) versus the alternative hypothesis H_a ($\mu_d \neq 0$), where μ_d was the mean change from baseline to Day 14. If the assumptions for the parametric test were not met, the nonparametric test (Wilcoxon signed rank test) was used. The Shapiro-Wilk test was used to test the normality.

Summary statistics was provided for the percentage of subjects achieving the clinical response threshold at Day 14 (i.e., 3 secondary efficacy endpoints) and for exploratory efficacy endpoints that were categorical for all other time points. For QMG, MG Composite, and MG-ADL as continuous variables, a paired *t* test or Wilcoxon signed rank test was used for testing the treatment effect (if applicable) at different visits for change from baseline in QMG, MG Composite, and MG-ADL.

All descriptive statistics was calculated in SAS® version 9.4 or higher. All statistical inferences on efficacy data analyses were tested 2-sided with $\alpha = 0.05$, if applicable.

Results

Forty-nine subjects were recruited and participated in the study from June 1, 2015 through April 17, 2018. All 49 enrolled subjects were analyzed for safety, and 43 were evaluated for efficacy. Of the 6 subjects excluded from the Evaluable population, 4 received IGIV-C on the first infusion day only with none ($n = 3$) or very little ($n = 1$) infused on the second dosing day due to non-serious AEs; 2 violated inclusion criteria either due to clinical presen-

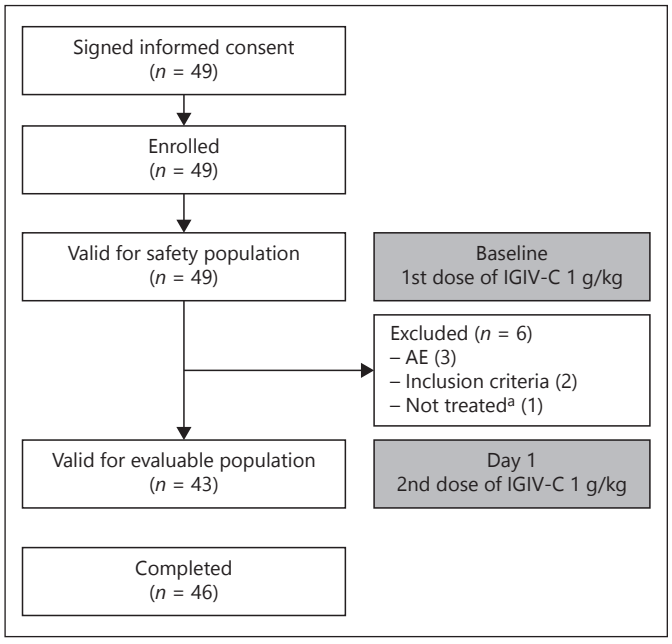

Fig. 1. Subject disposition. AE, adverse event; IGIV-C, immune globulin caprylate/chromatography purified. [a] Did not receive a full dose on Day 1 due to AEs of vomiting and nausea.

tation inconsistent with MG exacerbation (QMG = 6) or fewer than 8 weeks CS MG treatment. Subject disposition in shown in Figure 1.

Demographics and Baseline Characteristics

Demographic and baseline disease characteristics are summarized in Table 1. Subjects were predominantly female (69.4%) and White (89.8%), with a median age of 47.0 years and median time since MG diagnosis of 5.4 years. No subjects were MuSK-antibody positive. Details of historical testing establishing the diagnosis of MG are included in Table 1.

Efficacy

At Baseline, median QMG, MG Composite, and MG-ADL scores were 22, 30, and 14 points, respectively, indicating significant MG-related weakness. For the primary efficacy endpoint in the Evaluable population, there was a significant decrease in mean ± SD QMG from Baseline to Day 14 (–6.4 ± 5.15, $p < 0.001$, 95% CI –7.957 to –4.787); results in the Safety population were comparable. A significant decrease in QMG was evident at Day 7 and became increasingly pronounced at Day 21. Efficacy data are summarized in Table 2 for all efficacy scales analyzed as continuous variables. Figure 2 provides illustrations of mean change from baseline for QMG, MG Composite, and MG-ADL scores for the Evaluable population at all study time points.

Of the 43 subjects assessed on the secondary efficacy endpoints, 33 (76.7%) achieved a clinical response as measured by QMG, 37 (86.0%) surpassed the response threshold on the MG Composite, and 38 (88.4%) achieved a response on the MG-ADL. Categorical responses at all time points are illustrated in Figure 3.

In the exploratory efficacy analyses, the mean QMG changes from baseline were –4.7, –6.4, –7.9, and –7.8 at Days 7, 14, 21, and 28, respectively. The mean changes from baseline in MG Composite score were –7.8, –12.1, –13.6, and –13.7 at Days 7, 14, 21, and 28, respectively. For MG-ADL, the respective mean changes from baseline were –4.2, –6.2, –7.0, and –7.0 at Days 7, 14, 21, and 28. Similar results for all exploratory analyses of efficacy parameters were observed in the Safety population.

For all 3 efficacy parameters, response was robust at Day 7, improved at Days 14 and 21, and remained evident at the last time point on Day 28. Group mean and median MG Composite and MG-ADL scores were substantially reduced to approximately 50–60% of their entry value by Day 14 in Evaluable and Safety populations, and group median values were half of entry median scores at Day 28.

Following IGIV-C administration, AChR antibody levels decreased; no subjects became negative for anti-AChR (data not shown).

Safety

Of the 49 subjects in the Safety population, 39 (79.6%) reported treatment-emergent AEs (TEAEs). The most frequent TEAEs in these subjects were headache 19 (38.8%), pyrexia 8 (16.3%), urticaria 4 (8.2%), influenza-like illness 3 (6.1%), rash 3 (6.1%), and vomiting 3 (6.1%). Most TEAEs were mild or moderate. There were no serious AEs and no thromboembolic events. Three subjects discontinued study prematurely and did not receive the second day of IGIV-C infusion due to mild or moderate non-serious AEs that fully resolved within 1 day (rash pruritic $n = 1$ subject, urticaria $n = 1$ subject, and 1 subject with hypersensitivity manifesting as facial hyperemia, back pain, headache, myalgia, and pyrexia). A summary of TEAEs is provided in Table 3.

Routine clinical laboratory parameters (chemistry, hematology, and urinalysis) and vital signs data showed no consistent treatment-emergent pattern of abnormality. Twenty-one subjects (42.9%) had a positive DAT after IGIV-C administration, but these results were transient in some cases and not sustained. Five subjects (10.2%)

Table 1. Subject demographics and disease characteristics[a]

Gender, *n* (%)	
Female	34 (69.4)
Male	15 (30.6)
Age, years	
Mean ± SD	47.3±15.22
Median (range)	47.0 (18–82)
Weight, kg	
Mean ± SD	71.9±16.01
Median (range)	70.0 (40.0–104.0)
Race, *n* (%)	
White	44 (89.8)
Black or African American	2 (4.1)
Asian	1 (2.0)
American Indian or Alaska Native	1 (2.0)
Unknown	1 (2.0)
MGFA classification at enrollment, *n* (%)	
IVb	49 (100)
V	0 (0)
Time since initial MG diagnosis, years	
Mean ± SD	7.85±8.90
Median (range)	5.36 (0.15–39.18)
Historical test performed to confirm MG diagnosis[b], *n* (%)	
Edrophonium chloride test or equivalent	15 (30.6)
Acetylcholine receptor antibody test positive	29 (59.2)
Single-fiber EMG or electrodiagnostic test[c] diagnostic/consistent with MG	39 (79.6)
Time since last MG exacerbation, years	
Mean ± SD (*n* = 44)	1.37±2.2128
Median (range) (*n* = 44)	0.26 (0.01–11.18)

[a] (*n* = 49) subjects unless otherwise specified.
[b] Diagnostic options are not mutually exclusive.
[c] Such as repetitive nerve stimulation.
MG, myasthenia gravis; MGFA, MG Foundation of America; EMG, electromyography.

fulfilled a prospectively defined hemolysis algorithm (i.e., positive DAT with ≥1 g/dL decreased hemoglobin and 2 additional laboratory markers of potential hemolysis). For 3 of these 5 subjects, anemia (hemoglobin < lower normal limit) resulted in nadir of values 9.62, 11.8, and 12.0 g/dL, corresponding to decreases of 2.6, 3.3, and 1.6 g/dL from prior visit. Two subjects had TEAEs of anemia considered potentially related to IGIV-C of mild intensity with full recovery.

Discussion

This multicenter, prospective, open-label, non-controlled clinical trial was conducted to assess the efficacy and safety of IGIV-C in subjects with MG exacerbations producing significant disability (MGFA IVb or V). Results show that clinically meaningful improvement was observed for all efficacy parameters. Specifically, for the primary endpoint, there was a significant decrease in QMG scores from Baseline to Day 14 in the Evaluable population. Secondary endpoints all showed an efficacy benefit in the majority of Evaluable subjects (≥76.7% responders at Day 14). Among the exploratory endpoints, a profound decrease in MG Composite and MG-ADL total score was shown by the 50–60% reduction in group median entry values by Day 14. There were no safety issues or specific laboratory trends of interest related to study drug infusion, except for positive DAT with reversible decreased hemoglobin in a few subjects. In this study, therefore, IGIV-C was effective, safe, and well tolerated in the treatment of patients with MG exacerbations.

These findings appear robust in the context of the literature data for IVIG in MG worsening and MG exacerbations [11, 15, 19–22]. For example, Zinman et al [19, 21] evaluated IGIV-C 2 g/kg versus placebo in 51

Table 2. Analysis of change in QMG, MG composite, MG-ADL (Evaluable population, $n = 43$)

Measure	Day	Baseline score		Change from Baseline		p value[a]	95% CI of mean change
		mean ± SD	median (min – max)	mean ± SD	median (min – max)		
QMG	0	22.0±4.60	22.0 (14 to 33)	–	–	–	–
	7	17.5±5.17	17.0 (1 to 29)	–4.7±4.58	–4.0 (–21 to –4)	<0.001	–
	14	15.6±5.14	16.0 (4 to 27)	–6.4±5.15	–6.0 (–15 to –8)	<0.001	–7.957 to –4.787
	21	14.1±4.73	15.0 (0 to 23)	–7.9±5.78	–8.0 (–22 to –4)	<0.001	–9.686 to –6.128
	28	14.2±5.22	15.0 (0 to 24)	–7.8±5.71	–8.0 (–22 to –4)	<0.001	–9.572 to –6.056
MG composite	0	28.9±6.80	30.0 (16 to 42)	–	–	–	–
	7	21.5±7.71	20.0 (0 to 37)	–7.8±6.95	–6.0 (–31 to –3)	<0.001	–
	14	16.8±7.03	18.0 (2 to 31)	–12.1±7.72	–11.0 (–32 to –2)	<0.001	–14.514 to –9.765
	21	15.3±7.34	16.0 (0 to 32)	–13.6±8.70	–12.0 (–32 to –5)	<0.001	–16.237 to –10.879
	28	15.3±6.97	15.0 (0 to 33)	–13.7±8.38	–12.0 (–32 to –4)	<0.001	–16.231 to –11.071
MG-ADL	0	13.8±3.96	14.0 (6 to 20)	–	–	–	–
	7	9.7±4.66	9.0 (0 to 19)	–4.2±3.31	–4.0 (–14 to –3)	<0.001	–5.223 to –3.158
	14	7.6±4.15	7.0 (1 to 15)	–6.2±3.87	–6.0 (–16 to –2)	<0.001	–7.400 to –5.018
	21	6.8±3.93	7.0 (0 to 13)	–7.0±4.14	–6.0 (–16 to –3)	<0.001	–8.252 to –5.702
	28	6.8±3.81	6.0 (0 to 14)	–7.0±4.41	–7.0 (–15 to –3)	<0.001	–8.334 to –5.619

[a] Calculated from paired t test.
MG, myasthenia gravis; QMG, qualtitative MG test; MG-ADL, MG-activities of daily living.

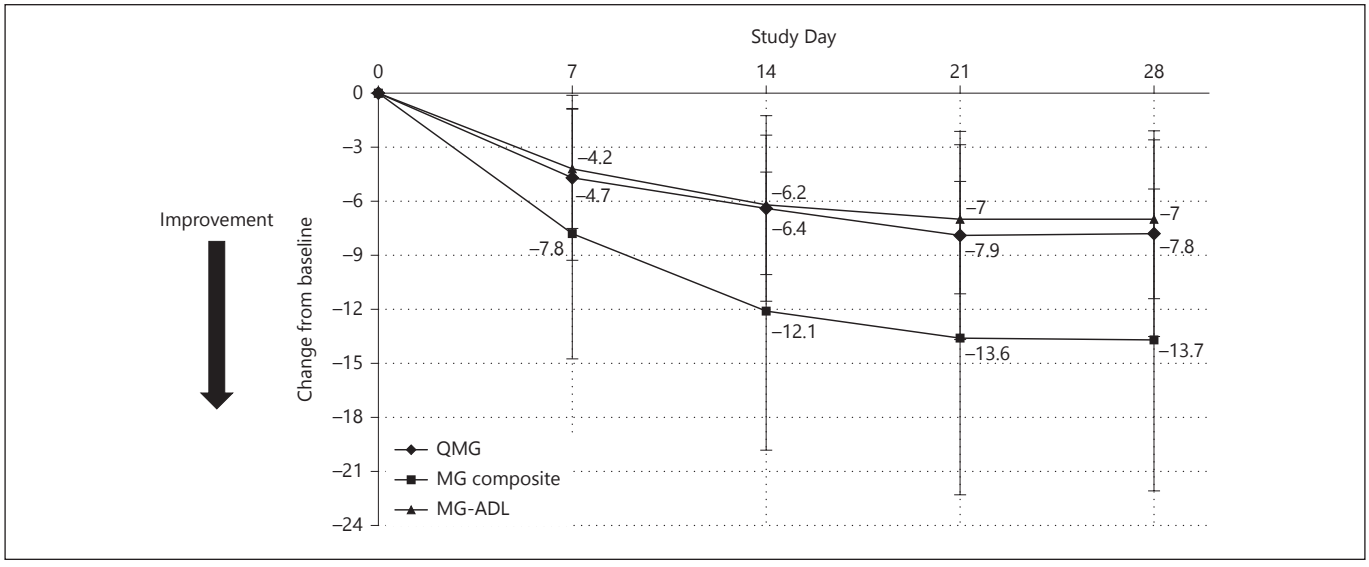

Fig. 2. Mean QMG, MG Composite, and MG-ADL change from Baseline by time point (evaluable population, $n = 43$, mean, SD). MG, myasthenia gravis; QMG, quantitative MG; MG-ADL, MG-activities of daily living.

subjects and showed a mean change in QMG at Day 14 of –2.54 in the IGIV-C group versus –0.89 for placebo ($p = 0.047$); a more pronounced treatment effect was observed in subjects with QMG scores >10.5 prior to treatment with IGIV (–4.10 vs. –0.71, $p = 0.010$). Other work comparing 2 g/kg IGIV-C with PLEX in 84 subjects with QMG scores >10.5 at study entry found mean ± SD changes from baseline in QMG score of –3.2 ± 4.1 points for IGIV-C and –4.7 ± 4.9 points for PLEX ($p = 0.13$) at Day 14, providing evidence that IVIG and

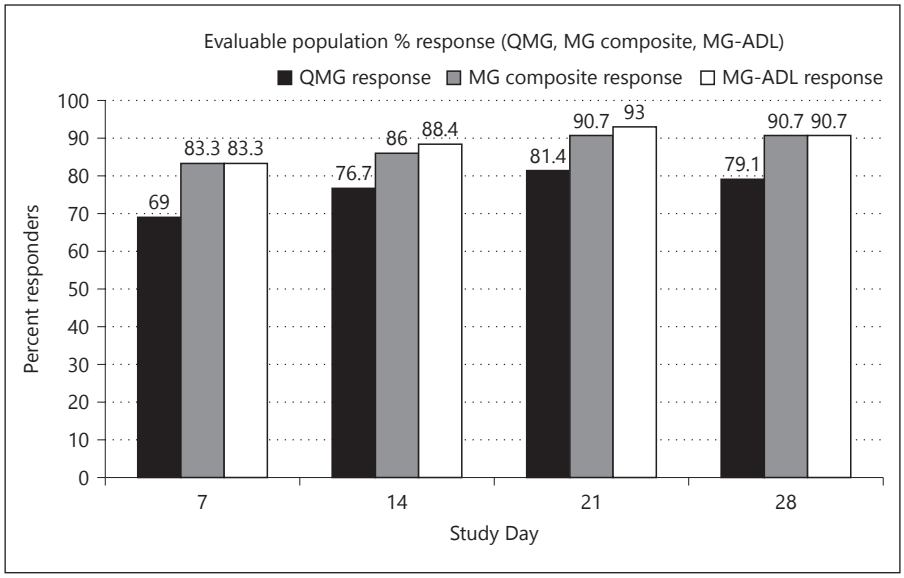

Fig. 3. Proportion of responders[a] assessed by QMG, MG Composite, and MG-ADL by time point (evaluable population, n = 43). [a] Defined as at least a 3-point decrease for QMG and MG Composite and at least a 2-point decrease for MG-ADL from Baseline to Day 14. MG, myasthenia gravis; QMG, quantitative MG; MG-ADL, MG-Activities of Daily Living.

Table 3. Treatment-emergent AEs by subject irrespective of relationship to study drug (≥5% of subjects)

MedDRA system organ class and preferred term	Subjects (n = 49), n (%)	Events (n = 98), n (%)
Any treatment-emergent AE	39 (79.6)	98 (100.0)
Nervous system disorders	21 (42.9)	23 (23.5)
Headache	19 (38.8)	21 (21.4)
General disorders and administration site conditions	13 (26.5)	14 (14.3)
Pyrexia	8 (16.3)	9 (9.2)
Influenza like illness	3 (6.1)	3 (3.1)
Skin and subcutaneous tissue disorders	10 (20.4)	11 (11.2)
Urticaria	4 (8.2)	4 (4.1)
Rash	3 (6.1)	4 (4.1)
Gastrointestinal disorders	4 (8.2)	7 (7.1)
Vomiting	3 (6.1)	3 (3.1)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

PLEX are comparably effective in adults with moderate to severe MG within 2 weeks of treatment [20]. An open-label study evaluating IVIG and PLEX in 87 subjects with MG exacerbations also found no significant difference in efficacy; at Day 15, the mean change in Myasthenic Muscular Score was 15.6 (95% CI 10.9–20.3) in the IVIG group and 16.6 (95% CI 11.6–21.6) in the PLEX group (p = 0.65) [11]. Another double-blind randomized trial comparing IVIG 2 g/kg with IVIG 1 g/kg for MG acute exacerbations in 173 subjects showed that the mean Myasthenic Muscular Score change in both IVIG dose groups was similar (effect size difference = 3.84; 95% CI –1.03 to 8.71; p = 0.12) [22, 26].

The present Phase 3 study was a single-arm clinical trial designed specifically to confirm the efficacy of IGIV-C 2 g/kg in MG exacerbations (≥ MGFA IVb severity). Results were commensurate with improvements observed in randomized, controlled clinical trials of IVIG in MG worsening/MG exacerbations, and the magnitude of treatment effect was impactful and clinically significant. The results of this study support IGIV-C as treatment of severe MG exacerbations requiring hospitalization.

The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Statement of Ethics

The study protocol was approved by Institutional Review Boards/Independent Ethics Committees/Research Ethics Boards at all participating institutions (see Supporting Information for full listing) and by regulatory authorities. It was registered at ClinicalTrials.gov (NCT02413580) and European Clinical Trials Register (EudraCT number 2013-005098-28). All patients provided written informed consent, and the investigators ensured that all study-related activities were conducted in full conformance with appropriate local laws, regulations, International Conference on Harmonisation Good Clinical Practice, and the Declaration of Helsinki.

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Disclosure statement

Bleeker reports receiving financial compensation from Grifols for the conduct of this study; P.V.D. reports non-financial support from CSL Behring, Pfizer, and Alexion Pharmaceuticals outside the submitted work; J.M.H. reports non-financial support from University of Cape Town during the conduct of the study; V.B. reports receiving grants from the University Health Network during the conduct of the study, grants and personal fees from CSL Behring, UCB, Octapharma, Takeda (Shire, Baxalta), Alnylam, personal fees from Akcea and Pfizer outside the submitted work; E.M. reports being an employee of Grifols Therapeutics LLC; R.G. reports being an employee of Grifols Therapeutics LLC; J.C. reports being an employee of Grifols Therapeutics LLC; W.H. reports being an employee of Grifols Therapeutics LLC; Garcia reports being an employee of Grifols Therapeutics LLC; S.C. reports being an employee of Grifols Therapeutics LLC; J.A. reports being an employee of Grifols Therapeutics LLC.

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