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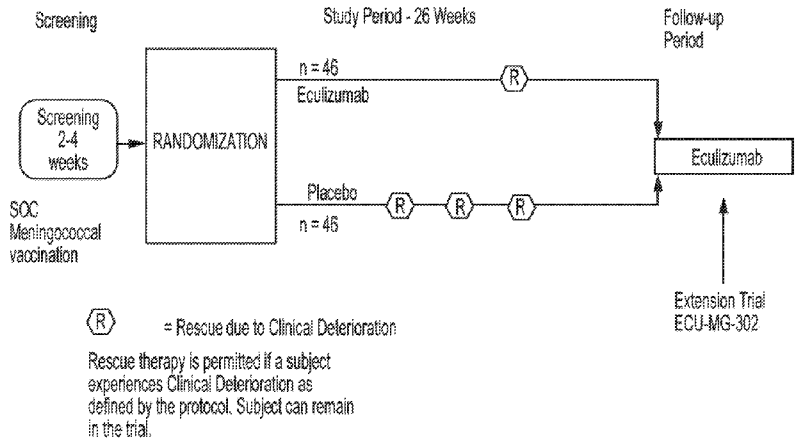

Fig. 1

(57) Abstract: The disclosure provides methods of treating myasthenia gravis (MG) in a subject in need thereof by administering to the subject a substance that specifically binds complement component 5 (C5). In certain embodiments, the substance that specifically binds C5 is a binding protein, such as an anti-C5 antibody.

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METHODS FOR TREATMENT OF REFRACTORY GENERALIZED MYASTHENIA GRAVIS

BACKGROUND

Myasthenia Gravis (MG) is a rare, debilitating, acquired autoimmune neurologic disorder of the neuromuscular junction (NMJ) caused by the failure of neuromuscular transmission, which results from the binding of auto-antibodies (Abs) to proteins involved in signaling at the NMJ. These proteins include the nicotine acetylcholine receptors (AChRs) or, less frequently, a muscle-specific tyrosine kinase (MuSK) involved in AChR clustering.

MG has a prevalence of 14-20 per 100,000 in the U.S., affecting roughly 60,000 Americans. It affects males and females in equal ratio, although the incidence in females peaks in the 3rd decade as compared to males in whom the peak age at onset is in the 6th or 7th decade. Mortality from MG is approximately 4%, mostly due to respiratory failure.

Myasthenia gravis is clinically characterized by weakness and fatigability of voluntary skeletal muscles. MG may initially present with ocular muscle weakness affecting eye and eyelid movement, referred to as ocular MG (oMG). Ten percent of subjects have disease limited to ocular muscles. Ninety percent of subjects have generalized MG, with muscle weakness involving neck, head, spine, bulbar, respiratory, or limb muscles. Bulbar weakness refers to muscles controlled by nerves originating from the bulb-like part of the brainstem and manifests as difficulty in talking, chewing, swallowing, and control of the head. MG may cause life-threatening respiratory failure, referred to as myasthenic crisis. About 15% to 20% of subjects will experience a myasthenic crisis during the course of their disease, 75% within 2 years of diagnosis, requiring hospitalization and ventilatory support.

While there is no cure for MG, there are a variety of therapies that reduce muscle weakness and improve neuromuscular function. Current available treatments for myasthenia gravis aim to modulate neuromuscular transmission, inhibit the production or effects of pathogenic antibodies, or inhibit inflammatory cytokines. There is currently no specific treatment that targets the underlying pathophysiology of NMJ injury specifically: anti-AChR antibody-AChR interactions resulting in complement activation via the classical pathway and inflammation, with the resultant destruction of the NMJ. There is no specific treatment that corrects the autoimmune defect in MG. With immunosuppressive therapies (ISTs) the current standard of care, which usually combines cholinesterase inhibitors, corticosteroids and

immunosuppressive drugs (most commonly azathioprine [AZA], cyclosporin, and mycophenolate mofetil [MMF]), the majority of subjects with MG have their disease reasonably well controlled. However, there is a cohort of refractory subjects who do not respond adequately to ISTs, or cannot tolerate ISTs, and those who require repeated treatments with plasma exchange (PE) and/or intravenous immunoglobulin (IVIg) to maintain clinical stability. For these subjects, an alternative therapy is needed.

SUMMARY

This disclosure provides methods of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering a therapeutically effective amount of an anti-complement component 5 (C5) antibody or an antigen binding fragment thereof to the patient, wherein the patient is administered the anti-C5 antibody or antigen binding fragment thereof for at least 26 weeks.

In certain embodiments, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering a therapeutically effective amount of an anti-C5 antibody or an antigen binding fragment thereof to the patient, wherein the anti-C5 antibody, or an antigen binding fragment thereof is eculizumab or an eculizumab variant and wherein the patient is administered eculizumab or eculizumab variant for at least 26 weeks.

In another embodiment, this disclosure provides a method comprising administering a therapeutically effective amount of eculizumab to a patient, wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability; and wherein the patient is administered eculizumab for at least 26 weeks.

In one embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient, wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and had previously failed treatment with

at least two immunosuppressive agents or failed treatment with at least one immunosuppressive agent and required chronic plasma exchange or IVIg, and had an MG-ADL total score ≥6 at study entry; wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg as a fifth induction dose on day 28, wherein the patient is administered eculizumab for at least 26 weeks; wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter, and wherein the patient has a clinically meaningful improvement (reduction) in two measurements of generalized myasthenia gravis severity selected from the group consisting of MG-ADL, QMG, and MGC.

In a particular embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient, wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) or requires chronic plasma exchange or chronic IVIg to maintain clinical stability; wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg of eculizumab as a fifth induction dose on day 28, and wherein the patient is administered eculizumab for at least 26 weeks.

In a further embodiment, this disclosure provides a method wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and 1200 mg of eculizumab every 14 ± 2 days thereafter.

In certain embodiments, this disclosure provides a method wherein the dosing regimen further comprises a third phase and wherein the third phase comprises performing plasmapheresis on the patient and administering eculizumab at a dose of between 300 and 1200 mg to the patient within 4 hours of completion of plasmapheresis. In other embodiments, the third phase comprises performing plasmapheresis on the patient and administering eculizumab at a dose of between 600 and 900 mg to the patient within 90 minutes of completion of

plasmapheresis. In yet other embodiments, the third phase comprises performing plasmapheresis on the patient and administering eculizumab at a dose of 600 mg to the patient within 1 hour of completion of plasmapheresis.

In one embodiment, the patient being treated by the methods provided herein experiences a clinically meaningful improvement (reduction) in Myasthenia Gravis Activities of Daily Living (MG-ADL) score after 26 weeks of treatment. In a particular embodiment, the clinically meaningful improvement the patient experiences is at least a 3 point reduction in the patient's MG-ADL score after 26 weeks of treatment. In another embodiment, the clinically meaningful improvement the patient experiences is at least a 4 point reduction in the patient's MG-ADL score after 26 weeks of treatment.

In another embodiment, the patient being treated by the methods provided herein experiences a clinically meaningful improvement (reduction) in quantitative Myasthenia Gravis score (QMG) after 26 weeks of treatment. In a particular embodiment, the clinically meaningful improvement the patient experiences is at least a 4 point reduction in the patient's QMG score after 26 weeks of treatment. In another embodiment, the clinically meaningful improvement the patient experiences is a 5 point reduction in the patient's QMG score after 26 weeks of treatment.

In another embodiment, the patient being treated by the methods provided herein experiences a clinically meaningful improvement (reduction) in Myasthenia Gravis Composite (MGC) score after 26 weeks of treatment. In a particular embodiment, the clinically meaningful improvement the patient experiences is at least a 6 point reduction in the patient's MGC score after 26 weeks of treatment. In another embodiment, the clinically meaningful improvement the patient experiences is at least a 10 point reduction in the patient's MGC score after 26 weeks of treatment.

In another embodiment, the patient being treated by the methods provided herein experiences a clinically meaningful improvement (reduction) in quality of life as measured by the Myasthenia Gravis Quality of Life (MG-QOL-15) score after 26 weeks of treatment. In a particular embodiment, the clinically meaningful improvement the patient experiences is at least a 6 point reduction in the patient's MG-QOL-15 score after 26 weeks of treatment. In another embodiment, the clinically meaningful improvement the patient experiences is at least an 11 point reduction in the patient's MG-QOL-15 score after 26 weeks of treatment.

In another embodiment, the patient being treated by the methods provided herein experiences a clinically meaningful improvement (reduction) in neuro-fatigue as measured by the Neuro-QOL Fatigue score after 26 weeks of treatment. In a particular embodiment, the clinically

meaningful improvement the patient experiences is at least an 8 point reduction in the patient's Neuro-QOL score after 26 weeks of treatment. In another embodiment, the clinically meaningful improvement the patient experiences is at least a 16 point reduction in the patient's Neuro-QOL score after 26 weeks of treatment.

In a certain embodiment, the patient being treated by the methods provided herein experiences a clinically meaningful improvement (increase) in health status as measured by the EQ-5D health status score after 26 weeks of treatment.

In a particular embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient, wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) or requires chronic plasma exchange or chronic IVIg to maintain clinical stability; wherein eculizumab is administered using a phased dosing schedule comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg of eculizumab as a fifth dose on day 28, wherein the patient is administered eculizumab for at least 26 weeks; wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter, and wherein the patient has a clinically meaningful improvement (reduction) in at least one measurement of generalized myasthenia gravis severity selected from the group consisting of MG-ADL, QMG, MGC, MG-QOL, and Neuro-QOL.

In another embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient, wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability; wherein eculizumab is administered using a phased dosing schedule comprising administering a 900 mg induction dose on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg of eculizumab as a fifth dose on day 28, wherein the patient is administered eculizumab

for at least 26 weeks; wherein the 28 induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter, and wherein the patient has a clinically meaningful improvement (reduction) in two measurements of generalized myasthenia gravis severity selected from the group consisting of MG-ADL, QMG, MGC, MG-QOL, and Neuro-QOL.

In another embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient, wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) or requires chronic plasma exchange or chronic IVIg to maintain clinical stability; wherein eculizumab is administered using a phased dosing schedule comprising administering a 900 mg induction dose on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg as a fifth dose on day 28, wherein the patient is administered eculizumab for at least 26 weeks; wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter, and wherein the patient has a clinically meaningful improvement (reduction) in three measurements of generalized myasthenia gravis severity selected from the group consisting of MG-ADL, QMG, MGC, MG-QOL, and Neuro-QOL. In certain embodiments, the patient has a clinically meaningful improvement (reduction) in four measurements of generalized myasthenia gravis severity selected from the group consisting of MG-ADL, QMG, MGC, MG-QOL, and Neuro-QOL. In another embodiment, the patient has a clinically meaningful improvement (reduction) in five measurements of generalized myasthenia gravis severity, wherein the five measurements of generalized myasthenia gravis severity are MG-ADL, QMG, MGC, MG-QOL, and Neuro-QOL.

In another embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient, wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while therapy for myasthenia gravis including anticholinesterase

inhibitor therapy and immunosuppressant therapy (IST) or requires chronic plasma exchange or chronic IVIg to maintain clinical stability; wherein eculizumab is administered using a phased dosing schedule comprising administering a 900 mg induction dose on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg as a fifth dose on day 28, wherein the patient is administered eculizumab for at least 26 weeks; wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg every 14 ± 2 days thereafter, and wherein the patient has a clinically meaningful improvement (reduction) in five measurements of generalized myasthenia gravis severity, wherein the five measurements of generalized myasthenia gravis severity are a reduction in MG-ADL of at least 3 points, a reduction in QMG of at least 4 points, a reduction in MGC of at least 6 points, a reduction in MG-QOL of at least 6 points, and a reduction in Neuro-QOL of at least 8 points. In certain embodiments, the patient has a clinically meaningful improvement (reduction) in five measurements of generalized myasthenia gravis severity, wherein the five measurements of generalized myasthenia gravis severity are a reduction in MG-ADL of at least 4 points, a reduction in QMG of at least 5 points, a reduction in MGC of at least 10 points, a reduction in MG-QOL of at least 11 points, and a reduction in Neuro-QOL of at least 16 points.

In a further embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab by intravenous infusion. In another embodiment, eculizumab is administered subcutaneously. In another embodiment, the eculizumab comprises a heavy chain amino acid sequence according to SEQ ID NO: 10 and a light chain amino acid sequence according to SEQ ID NO: 11. In yet another embodiment, the eculizumab is an eculizumab variant comprising a heavy chain amino acid sequence according to SEQ ID NO: 14 and a light chain amino acid sequence according to SEQ ID NO: 11. In certain embodiments, the eculizumab is an eculizumab variant comprising a heavy chain variable region amino acid sequence according to SEQ ID NO: 12 and a light chain amino acid sequence according to SEQ ID NO: 11.

In yet another embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering an anti-C5 antibody, or antigen binding fragment thereof, wherein the antibody is an anti-C5 antibody or an antigen binding fragment thereof comprising a heavy chain variable region amino acid sequence according to SEQ ID NO: 27 and a light chain variable region amino acid sequence according to SEQ ID NO: 28. In yet another embodiment, the antibody is an anti-C5 antibody or an antigen

binding fragment thereof comprising a heavy chain variable region amino acid sequence according to SEQ ID NO: 35 and a light chain variable region amino acid sequence according to SEQ ID NO: 36. In yet another embodiment, the antibody is an anti-C5 antibody or antigen binding fragment thereof comprising a heavy chain variable region amino acid sequence according to SEQ ID NO: 37 and a light chain variable region amino acid sequence according to SEQ ID NO: 38.

In one embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering an anti-C5 antibody or antigen binding fragment thereof, wherein the patient has failed treatment over one year or more with two or more ISTs in sequence or in combination.

In one embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering an anti-C5 antibody or antigen binding fragment thereof, wherein the patient has failed at least one IST and requires chronic plasma exchange or IVIg to control symptoms of myasthenia gravis.

In one embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering a therapeutically effective amount of eculizumab is maintained at a concentration of between 50-100 μg/mL in the patient's serum.

In one embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering a therapeutically effective amount of eculizumab, wherein the patient experiences a discontinuation in the administration of one or more IST following at least 26 weeks of treatment.

In one embodiment, this disclosure provides a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering a therapeutically effective amount of eculizumab, wherein the patient experiences a reduction in IST dosing following at least 26 weeks of treatment.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic of the overall design of the clinical trial disclosed herein.

Figures 2A and 2B are a schematic of the EUROQOL (EQ-5D) survey of health status questionnaire used in the clinical trial disclosed herein.

Figure 3 is a schematic of the *N. meningitidis* vaccination schedule used in the clinical trial disclosed herein.

Figure 4 is a schematic of the dosing schedule used in the clinical trial disclosed herein.

Figure 5 is a schematic of the dosing, clinical evaluation and safety follow-up schedule, used in the clinical trial disclosed herein.

Figure 6 is a schematic of the dosing schedule used in the clinical trial also including the extension period disclosed herein.

Figure 7 is a graphical depiction of the changes from baseline in MG-ADL values obtained for placebo and eculizumab groups over the initial 26 weeks of the trial.

Figure 8 is a graphical depiction of the changes from baseline in QMG values obtained for placebo and eculizumab groups over the initial 26 weeks of the trial.

Figure 9 is a graphical depiction of the changes from baseline in MGC values obtained for placebo and eculizumab groups over the initial 26 weeks of the trial.

Figure 10 is a graphical depiction of the changes from baseline in MG-QOL 15 values obtained for placebo and eculizumab groups over the initial 26 weeks of the trial.

Figure 11 is a graphical depiction of the numbers of patients in both the placebo and eculizumab treated groups achieving between a 5 and 10 point reduction in QMG score over the initial 26 weeks of the trial.

Figure 12 is a schematic of the REGAIN study design.

Figure 13 is a graphical depiction of responder analyses (MG-ADL and QMG) illustrating the proportion of patients with improvement in total score and no rescue therapy at week 26 from baseline.

Figure 14 is a graphical depiction of the proportion of patients with a $\geq$3, $\geq$5, or $\geq$8-point reduction in MG-ADL total score and no rescue therapy over time from baseline to week 26.

Figure 15 is a graphical depiction of the proportion of patients with $\geq$5, $\geq$7, or $\geq$10-point reduction in QMG total score and no rescue over time from baseline to week 26.

Figure 16 is a graphical depiction of dual responders (assessed by MG-ADL and QMG total scores) with no rescue therapy at week 26.

Figure 17 is a graphical depiction of the proportion of patients with at least 3-point improvement in MG-ADL total score and $\geq$5-point improvement in QMG total score and no rescue therapy assessed over time from baseline to week 26.

Figure 18 is a graphical depiction of the percentage of patients who simultaneously met increasingly stringent criteria based on MG-ADL and QMG. The bottom row describes a threshold for both scales above the MCID (minimal clinically meaningful difference: 3 for MG-ADL and 5 for QMG). Higher bars represent increasing thresholds. The right-most panel

displays odds ratios for meeting each threshold for eculizumab vs. placebo treated patients.

Figure 19 is a graphical depiction of the change from baseline in MG-ADL total score (LS Mean and 95% CI) by treatment arm over time from ECU-MG-302 baseline to week 52 in study ECU-MG-302 using a repeated-measures model.

Figure 20 is a graphical depiction of the change from baseline in MG-ADL total score (Mean and 95% CI) by treatment arm over time from ECU-MG-301 baseline to week 52 in study ECU-MG-302.

DETAILED DESCRIPTION

The disclosure provides methods of treating myasthenia gravis (MG) in subjects or patients in need thereof by administering an antibody that specifically binds complement component 5 (C5). In certain embodiments, the antibody that specifically binds C5 reduces the rate at which C5 is cleaved, *in vivo*, into C5a and C5b. In other embodiments, the antibody that specifically binds C5, binds to one or both of the C5a and/or C5b fragments. In any of these embodiments, the antibody that specifically binds C5 blocks the complement cascade at C5, thereby reducing the release of proinflammatory mediators such as C5a and the formation of a C5b-9 Membrane Attack Complex (MAC).

In certain embodiments, the antibody that specifically binds C5 is eculizumab. In more specific embodiments, eculizumab is an antibody or a fragment thereof.

Eculizumab (h5G1.1-mAb) is a humanized monoclonal antibody (mAb) that was derived from the murine anti-human C5 antibody m5G1.1. Eculizumab specifically binds the terminal complement protein C5, thereby inhibiting its cleavage to C5a and C5b during complement activation. This strategic blockade of the complement cascade at C5 prevents the release of proinflammatory mediators and the formation of the Membrane Attack Complex or cytolytic pore, while preserving the early components of complement activation that are essential for the opsonization of microorganisms and clearance of immune complexes.

C5 binding proteins are described in U.S. Patent No. 6,355,245, which is hereby incorporated herein by reference in its entirety. In certain embodiments, the anti-C5 antibody is a monoclonal antibody having a hybrid IgG2/4 isotype. In other embodiments, the anti-C5 antibodies are effective in reducing the cell-lysing ability of complement present in human blood. This property of the antibodies can be determined by methods well known in the art such as, for example, by the chicken erythrocyte hemolysis method described in U.S. Patent No. 6,355,245.

In certain embodiments, anti-C5 antibodies bind to C5 or fragments thereof, *e.g.*, C5a or C5b. In other embodiments, the anti-C5 antibodies recognize and bind epitopes on either the alpha chain or the beta chain of purified human complement component C5 and are capable of blocking the conversion of C5 into C5a and C5b by C5 convertase. *See* Wurzner *et al.*, *Complement. Inflamm.* 8(5-6): 328-40 (1991).

In other embodiments, the anti-C5 antibodies recognize and bind epitopes within the alpha chain of purified human complement component C5. In this embodiment, the antibodies are capable of blocking the conversion of C5 into C5a and C5b by C5 convertase. In one example of this embodiment, the antibodies can provide this blockade at substantially the same concentrations needed to block hemolytic activity.

In some embodiments, the antibodies specifically bind to an amino-terminal region within the alpha chain, however, they do not specifically bind to free C5a. In certain embodiments, the C5 antibody is able to substantially inhibit complement hemolytic activity and to substantially inhibit the conversion of C5 to produce C5a. In some embodiments, the C5 antibodies provide these functions when used at a molar ratio of antibody to antigen (C5) of 3:1 or less.

As used herein, the term "antibodies" refers to immunoglobulins produced *in vivo*, as well as those produced *in vitro* by a hybridoma, and antigen binding fragments (*e.g.*, Fab' preparations) of such immunoglobulins, as well as to recombinantly expressed antibodies or antigen binding proteins, including immunoglobulins, chimeric immunoglobulins, "humanized" immunoglobulins, antigen binding fragments of such immunoglobulins, single chain antibodies, and other recombinant proteins containing antigen binding domains derived from immunoglobulins such as DVD-Ig and CODV-Ig. *See* U.S. Patent Nos. 7,161,181 and 9,181,349. "Specificity" refers to the ability of a binding protein to selectively recognize and bind an antigen at a particular location or structure, known as an epitope, often found on the surface of the antigen.

The term "specifically binds," means that a binding protein or fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by a dissociation constant of at least about $1x10^{-6}$ M or smaller. In other embodiments, the dissociation constant is at least about $1x10^{-7}$ M, $1x10^{-8}$ M, $1x10^{-9}$ M, or $1x10^{-10}$ M. Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like.

The anti-C5 antibodies described herein bind to complement component C5 (*e.g.*, human C5) and inhibit the cleavage of C5 into fragments C5a and C5b. Anti-C5 antibodies (or VH/VL domains derived therefrom) suitable for use in the invention can be generated using methods known in the art.

An exemplary anti-C5 antibody is eculizumab comprising heavy and light chains having the sequences shown in SEQ ID NOs: 10 and 11, respectively, or antigen binding fragments and variants thereof. Eculizumab (also known as SOLIRIS®) is described in U.S. Patent No. 6,355,245. Eculizumab is a humanized monoclonal antibody that is a terminal complement inhibitor.

In other embodiments, the antibody comprises the heavy and light chain complementarity determining regions (CDRs) or variable regions of eculizumab. Accordingly, in one embodiment, the antibody comprises the CDR1, CDR2, and CDR3 domains of the VH region of eculizumab having the sequence set forth in SEQ ID NO: 7, and the CDR1, CDR2, and CDR3 domains of the VL region of eculizumab having the sequence set forth in SEQ ID NO: 8. In another embodiment, the antibody comprises heavy chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 1, 2, and 3, respectively, and light chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 4, 5, and 6, respectively. In another embodiment, the antibody comprises VH and VL regions having the amino acid sequences set forth in SEQ ID NO: 7 and SEQ ID NO: 8, respectively.

Empirical data indicate that serum eculizumab concentrations greater than 50 μg/mL and closer to at least 100 μg/mL are required to significantly reduce free C5 concentrations. Specifically, free C5 concentration was reduced significantly with increasing concentrations of eculizumab beginning at >50 μg/mL and was at near zero levels with eculizumab concentrations above 100 μg/ml. Thus, in various embodiments, the method comprises administering a therapeutically effective amount of eculizumab to the subject, wherein the therapeutically effective amount of eculizumab is maintained at a concentration of at least 50 μg/mL of eculizumab in serum of the subject. In another embodiment, the method comprises administering a therapeutically effective amount of eculizumab to the subject, wherein the therapeutically effective amount of eculizumab is maintained at a concentration of at least 60 μg/mL of eculizumab in serum of the subject. In one embodiment, the method comprises administering a therapeutically effective amount of eculizumab to the subject, wherein the therapeutically effective amount of eculizumab is maintained at a concentration of at least 70 μg/mL of eculizumab in serum of the subject. In another embodiment, the method comprises administering

a therapeutically effective amount of eculizumab to the subject, wherein the therapeutically effective amount of eculizumab is maintained at a concentration of at least 80 μg/mL of eculizumab in serum of the subject. In another embodiment, the method comprises administering a therapeutically effective amount of eculizumab to the subject, wherein the therapeutically effective amount of eculizumab is maintained at a concentration of at least 90 μg/mL of eculizumab in serum of the subject. In another embodiment, the method comprises administering a therapeutically effective amount of eculizumab to the subject, wherein the therapeutically effective amount of eculizumab is maintained at a concentration of at least 100 μg/mL of eculizumab in serum of the subject.

Another exemplary anti-C5 antibody is an eculizumab variant, known as antibody BNJ441, and engineered to have a longer half-life (T1/2) in humans comprising heavy and light chains having the sequences shown in SEQ ID NOs: 14 and 11, respectively, or antigen binding fragments and variants thereof. BNJ441 (also known as ALXN1210) is described in International Publication No. WO 2015/134894 A1 and U.S. Patent No. 9,079,949, the teachings or which are hereby incorporated by reference. BNJ441 is a humanized monoclonal antibody that is structurally related to eculizumab (SOLIRIS®). BNJ441 selectively binds to human complement protein C5, inhibiting its cleavage to C5a and C5b during complement activation. This inhibition prevents the release of the proinflammatory mediator C5a and the formation of the cytolytic pore-forming membrane attack complex C5b-9 while preserving the proximal or early components of complement activation (*e.g.*, C3 and C3b) essential for the opsonization of microorganisms and clearance of immune complexes.

In other embodiments, the antibody comprises the heavy and light chain CDRs or variable regions of BNJ441. Accordingly, in one embodiment, the antibody comprises the CDR1, CDR2, and CDR3 domains of the VH region of BNJ441 having the sequence set forth in SEQ ID NO: 12, and the CDR1, CDR2, and CDR3 domains of the VL region of BNJ441 having the sequence set forth in SEQ ID NO: 8. In another embodiment, the antibody comprises heavy chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 19, 18, and 3, respectively, and light chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 4, 5, and 6, respectively. In another embodiment, the antibody comprises VH and VL regions having the amino acid sequences set forth in SEQ ID NO: 12 and SEQ ID NO: 8, respectively. In another embodiment, the antibody may comprise the heavy chain constant region of BNJ441 having the amino acid sequence set forth in SEQ ID NO: 13.

In various embodiments, eculizumab is administered in a multiphase dosing regimen. For

example, the multiphase dosing regimen comprises a first phase and a second phase in various embodiments. In certain embodiments, the first phase is an induction phase and comprises administration of eculizumab at between 900 mg once a week to the subject for between 1-10 weeks. The induction phase is concluded by administering the first maintenance phase dose of 1200 mg one week after the last 900 mg dose.

In other embodiments, the second phase is a maintenance phase and comprises administration of eculizumab at between 1000 and 1400 mg once every two weeks to the subject for 2 weeks, 4 weeks, 6 weeks, 8 weeks, 12, weeks, 26 weeks, or as long as myasthenia gravis persists. In other embodiments, the maintenance phase comprises administration of eculizumab at between 1000 and 1400 mg once every two weeks to the subject for 2 months, 4 months, 6 months, 8 months, 12 months, 2 years, three years, 4 years, 5 years, or for the remaining lifetime of the patient. In other embodiments, the maintenance phase comprises administration of eculizumab at about 1200 mg twice a month (biweekly) once the induction phase is complete.

In another embodiment, the method comprises administering a therapeutically effective amount of eculizumab or an eculizumab variant to the subject, wherein the therapeutically effective amount of eculizumab or eculizumab variant is maintained at a concentration of between 50-100 μg/mL, between 60-100 μg/mL, between 70-100 μg/mL, between 80-100 μg/mL, or between 90-100 μg/mL of eculizumab in serum of the subject.

Another exemplary anti-C5 antibody is antibody BNJ421 comprising heavy and light chains having the sequences shown in SEQ ID NOs: 20 and 11, respectively, or antigen binding fragments and variants thereof. BNJ421 (also known as ALXN1211) is described in International Publication No. WO 2015/134894 A1 and U.S. Patent No. 9,079,949, the teachings or which are hereby incorporated by reference.

In other embodiments, the antibody comprises the heavy and light chain CDRs or variable regions of BNJ421. Accordingly, in one embodiment, the antibody comprises the CDR1, CDR2, and CDR3 domains of the VH region of BNJ421 having the sequence set forth in SEQ ID NO: 12, and the CDR1, CDR2, and CDR3 domains of the VL region of BNJ421 having the sequence set forth in SEQ ID NO: 8. In another embodiment, the antibody comprises heavy chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 19, 18, and 3, respectively, and light chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 4, 5, and 6, respectively. In another embodiment, the antibody comprises VH and VL regions having the amino acid sequences set forth in SEQ ID NO: 12 and SEQ ID

NO: 8, respectively. In another embodiment, the antibody may comprise the heavy chain constant region of BNJ421 having the amino acid sequence set forth in SEQ ID NO: 9.

Another exemplary anti-C5 antibody is the 7086 antibody described in U.S. Patent Nos. 8,241,628 and 8,883,158. In one embodiment, the antibody may comprise the heavy and light chain CDRs or variable regions of the 7086 antibody. *See* U.S. Patent Nos. 8,241,628 and 8,883,158. In another embodiment, the antibody, or a fragment thereof, may comprise heavy chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 21, 22, and 23, respectively, and light chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 24, 25, and 26, respectively. In another embodiment, the antibody or fragment thereof may comprise the VH region of the 7086 antibody having the sequence set forth in SEQ ID NO: 27, and the VL region of the 7086 antibody having the sequence set forth in SEQ ID NO: 28.

Another exemplary anti-C5 antibody is the 8110 antibody also described in U.S. Patent Nos. 8,241,628 and 8,883,158. In one embodiment, the antibody may comprise the heavy and light chain CDRs or variable regions of the 8110 antibody. The antibody, or fragment thereof may comprise heavy chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 29, 30, and 31, respectively, and light chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 32, 33, and 34, respectively. In another embodiment, the antibody may comprise the VH region of the 8110 antibody having the sequence set forth in SEQ ID NO: 35, and the VL region of the 8110 antibody having the sequence set forth in SEQ ID NO: 36.

Another exemplary anti-C5 antibody comprises a heavy chain variable region amino acid sequence according to SEQ ID NO: 37 and a light chain variable region amino acid sequence according to SEQ ID NO: 38.

In various embodiments, eculizumab, an eculizumab variant such as BNJ441, or other anti-C5 antibody is administered to the subject once a month, once every two months, or once every three months depending on the dose. In another embodiment, the eculizumab, eculizumab variant such as BNJ441, or other anti-C5 antibody is administered once every two weeks, once a week, twice a week, or three times a week. In other embodiments, eculizumab, eculizumab variant such as BNJ441, or other anti-C5 antibody is administered once a week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, or once every eight weeks depending on the needs of the patient. In certain embodiments, eculizumab, eculizumab variant such as BNJ441, or other anti-C5 antibody in administered

intravenously (IV) or subcutaneously (SubQ).

Also, provided herein are pharmaceutical compositions comprising an anti-C5 antibody or antigen binding fragment thereof with a pharmaceutically acceptable excipient for treating MG. In one embodiment, the composition comprises an antibody comprising the CDR1, CDR2, and CDR3 domains of the VH region of eculizumab having the sequence set forth in SEQ ID NO: 7, and the CDR1, CDR2, and CDR3 domains of the VL region of eculizumab having the sequence set forth in SEQ ID NO: 8. In another embodiment, the antibody comprises heavy chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 1, 2, and 3, respectively, and light chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 4, 5, and 6, respectively. In another embodiment, the antibody comprises VH and VL regions having the amino acid sequences set forth in SEQ ID NO: 7 and SEQ ID NO: 8, respectively.

In some embodiment, the antibody comprises the heavy and light chain CDRs or variable regions of BNJ441. In one embodiment, the antibody comprises the CDR1, CDR2, and CDR3 domains of the VH region of BNJ441 having the sequence set forth in SEQ ID NO: 12, and the CDR1, CDR2, and CDR3 domains of the VL region of BNJ441 having the sequence set forth in SEQ ID NO: 8. In another embodiment, the antibody comprises heavy chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 19, 18, and 3, respectively, and light chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 4, 5, and 6, respectively. In another embodiment, the antibody comprises VH and VL regions having the amino acid sequences set forth in SEQ ID NO: 12 and SEQ ID NO: 8, respectively.

In some embodiment, the antibody comprises the heavy and light chain CDRs or variable regions of BNJ421. In one embodiment, the antibody comprises the CDR1, CDR2, and CDR3 domains of the VH region of BNJ421 having the sequence set forth in SEQ ID NO: 12, and the CDR1, CDR2, and CDR3 domains of the VL region of BNJ421 having the sequence set forth in SEQ ID NO: 8. In another embodiment, the antibody comprises heavy chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 19, 18, and 3, respectively, and light chain CDR1, CDR2, and CDR3 domains having the sequences set forth in SEQ ID NOs: 4, 5, and 6, respectively. In another embodiment, the antibody comprises VH and VL regions having the amino acid sequences set forth in SEQ ID NO: 12 and SEQ ID NO: 8, respectively.

1. Methods of Treating Myasthenia Gravis

The disclosure provides methods of treating subjects suffering from myasthenia gravis (MG) by administering an antibody that specifically binds C5. In other embodiments, the subject is a mammalian subject.

As used herein, the term "subject" and "patient" are interchangeable. In certain embodiments, subjects and/or patients are mammals. According to certain embodiments, primates include humans. Thus, in certain embodiments, the subjects or patients suffering from MG described herein are humans.

In certain embodiments, MG includes refractory generalized myasthenia gravis. In some embodiments, refractory generalized myasthenia gravis is characterized as including subjects or patients positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) who continue to show marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving current standard of care for myasthenia gravis such as cholinesterase inhibitor therapy and immunosuppressant therapy (IST) or who require chronic plasma exchange or chronic IVIg to maintain clinical stability. In other embodiments, refractory generalized myasthenia gravis is characterized as including subjects or patients who continue to show marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving current standard of care for myasthenia gravis such as cholinesterase inhibitor therapy and immunosuppressant therapy (IST) or who require chronic plasma exchange or chronic IVIg to maintain clinical stability.

In other embodiments, MG includes refractory generalized myasthenia gravis. In some embodiments, refractory generalized myasthenia gravis is characterized as including subjects or patients positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) who continue to show marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving cholinesterase inhibitor therapy and immunosuppressant therapy (IST) and who require chronic plasma exchange or chronic IVIg to maintain clinical stability. In other embodiments, refractory generalized myasthenia gravis is characterized as including subjects or patients who continue to show marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving cholinesterase inhibitor therapy and immunosuppressant therapy (IST) and who require chronic plasma exchange or chronic IVIg to maintain clinical stability.

As used herein, the phrase "requires chronic plasma exchange" to maintain clinical stability refers to the use of plasma exchange therapy on a patient on a regular basis for the

management of muscle weakness at least every 3 months over the last 12 months.

As used herein, the phrase "requires chronic IVIg" to maintain clinical stability refers to the use of IVIg therapy on a patient on a regular basis for the management of muscle weakness at least every 3 months over the last 12 months.

In certain embodiments, treatment of MG includes the amelioration or improvement of one or more symptoms associated with MG. Symptoms associated with MG include muscle weakness and fatigability. Muscles primarily affected by MG include muscles that control eye and eyelid movement, facial expressions, chewing, talking, swallowing, breathing, neck movements, and limb movements.

In other embodiments, treatment of MG includes the improvement of a clinical marker for MG progression. These markers include MG activity of daily living profile (MG-ADL), quantitative Myasthenia Gravis (QMG) score for disease severity, Myasthenia Gravis composite (MGC), negative inspiratory force (NIF), forced vital capacity, MGFA post-intervention status, and other quality of life measurements. In certain embodiments, MG-ADL is the primary score for measuring improvement of MG.

The MG-ADL is an 8-point questionnaire that focuses on relevant symptoms and functional performance of activities of daily living (ADL) in MG subjects (*see* Table 1). The 8 items of the MG-ADL were derived from symptom-based components of the original 13-item QMG to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb (2 items) impairment related to effects from MG. In this functional status instrument, each response is graded 0 (normal) to 3 (most severe). The range of total MG-ADL score is 0 – 24. A clinically meaningful improvement in a patient's MG-ADL would be a 3 point or greater reduction in score after 26 weeks of treatment.

The current QMG scoring system consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item); each graded 0 to 3, with 3 being the most severe (*see* Table 2). The range of total QMG score is 0 – 39. The QMG scoring system is considered to be an objective evaluation of therapy for MG and is based on quantitative testing of sentinel muscle groups. The MGFA task force has recommended that the QMG score be used in prospective studies of therapy for MG. A clinically meaningful improvement in a patient's QMG would be a 5 point or greater reduction in score after 26 weeks of treatment.

TABLE 1: MG ACTIVITY OF DAILY LIVING (MG-ADL) PROFILE

Items	Grade 0	Grade 1	Grade 2	Grade 3	Score (0,1,2,3)
1. Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric Tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric Tube	
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid drop	None	Occurs, but not daily	Daily, but not constant	Constant	

TABLE 2: QUANTITATIVE MG (QMG) SCORE FOR DISEASE SEVERITY

QUANTITATIVE MYASTHENIA GRAVIS TESTING FORM

Patient Name: _____ Patient #: _____ Date: _____
MR#: _____ DOB: _____ Sex: ____ Ht.(in): _____ Wt.(kg): _____
Evaluator: _____ Handedness: _____ Leggedness: _____ Time of Exam: _____
Anticholinesterase Medication: _____
Comments: _____

TEST ITEMS WEAKNESS	NONE	MILD	MODERATE	SEVERE	SCORE
GRADE	0	1	2	3	
Double vision (lateral gaze) Sec.	60	11-59	1-10	Spontaneous	
Ptosis (upward gaze) Sec.	60	11-59	1-10	Spontaneous	
Facial Muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
Swallowing 4 oz. Water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing Choking or nasal regurgitation	Cannot swallow (test not attempted)	
Speech following counting aloud from 1-50 (onset of dysarthria)	None at #50	Dysarthria at #30-49	Dysarthria at #10-29	Dysarthria at #9	
Right arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	
Left arm outstretched (90°, sitting) Sec.	240	90-239	10-89	0-9	
Forced vital capacity	≥80%	65-79%	50-64%	<50%	
Rt hand grip: male (Kg) : female	≥45 ≥30	15-44 10-29	5-14 5-9	0-4 0-4	
Left hand grip: male (Kg) : female	≥35 ≥25	15-34 10-24	5-14 5-9	0-4 0-4	
Head, lifted (45%, supine) Sec.	120	30-119	1-29	0	
Right leg outstretched (45-50%, supine) Sec.	100	31-99	1-30	0	
Left leg outstretched (45-50%, supine) Sec.	100	31-99	1-30	0	

TOTAL MG SCORE: _____

The MGC is a validated assessment tool for measuring clinical status of subjects with MG (16). The MGC assesses 10 important functional areas most frequently affected by MG and the scales are weighted for clinical significance that incorporates subject-reported outcomes. *See* Table 3. MGC will be administered at Screening, Day 1, Weeks 1-4, 8, 12, 16, 20, and 26 or ET (Visits 1-6, 8, 10, 12, 14, and 17 or ET). A clinically meaningful improvement in a patient's MGC would be a 3 point or greater reduction in score after 26 weeks of treatment.

TABLE 3: MG COMPOSITE SCALE

Ptosis, upward gaze (PE)	> 45 seconds	0	11-45 seconds	1	1-10 seconds	2	Immediate	3
Double vision on lateral gaze, left or right (PE)	> 45 seconds	0	11 – 45 seconds	1	1 – 10 seconds	2	Immediate	3
Eye closure (PE)	Normal	0	Mild weakness (can be forced open with effort)	1	Moderate weakness (can be forced open easily)	2	Severe weakness (unable to keep eyes closed)	3
Talking (Pt)	Normal	0	Intermittent slurring or nasal speech	1	Constant slurring or nasal but can be understood	2	Difficult to understand	3
Chewing (Pt)	Normal	0	Fatigue with solid food	1	Fatigue with soft food	2	Gastric tube	3
Swallowing (Pt)	Normal	0	Rare trouble or choking	1	Frequent trouble (change in diet)	2	Gastric tube	3
Breathing	Normal	0	SOB with exertion	1	SOB at rest	2	Ventilator	3
Neck Flex/Ext (weakest PE)	Normal	0	Mild	1	Moderate (~50% weak +/-15%)	2	Severe	3
Shoulder Abd (PE	Normal	0	Mild	1	Moderate (~50% weak +/-15%)	2	Severe	3
Hip flexion	Normal	0	Mild	1	Moderate (~50% weak +/-15%)	2	Severe	3
		0		11		22		33

The 15-item Myasthenia Gravis Qualify of Life 15 scale (MG-QOL 15) is a health-related quality of life evaluative instrument specific to subjects with MG. *See* Table 4. MG-QOL15 was designed to provide information about subjects' perception of impairment and disability and the degree to which disease manifestations are tolerated and to be easy to administer and interpret. The range of total scores is from 0 to 60. Higher scores translate into a greater extent of a patient's dissatisfaction with MG related dysfunction. The MG-QOL 15 is completed by the subject. Higher scores indicate greater extent of and dissatisfaction with MG-related dysfunction. A clinically meaningful improvement in a patient's MG-QOL 15 would be a decrease in score after 26 weeks of treatment.

TABLE 4: MYASTHENIA GRAVIS QUALIFY OF LIFE 15 SCALE (MG-QOL 15)

Statement: How true in past 4 weeks?	Not at all	A little bit	Somewhat	Quite a bit	Very Much
Frustrated by condition	0	1	2	3	4
Trouble using my eyes	0	1	2	3	4
Trouble eating	0	1	2	3	4
Condition limits social life	0	1	2	3	4
Condition limits hobbies/fun	0	1	2	3	4
Trouble meeting family's needs	0	1	2	3	4
Need to plan around condition	0	1	2	3	4
Occupational skills/job negatively affected	0	1	2	3	4
Difficulty speaking	0	1	2	3	4
Trouble driving	0	1	2	3	4
Depressed about condition	0	1	2	3	4
Trouble walking	0	1	2	3	4
Trouble getting around in public places	0	1	2	3	4
Feel overwhelmed by condition	0	1	2	3	4
Trouble performing personal grooming	0	1	2	3	4

The Neuro-QOL Fatigue is a reliable and validated brief 19-item survey of fatigue completed by the subject. Higher scores indicate greater fatigue and greater impact of MG on activities (*see* Table 5). A clinically meaningful improvement in a patient's Neuro-QQL Fatigue score would be reflected in a decrease in score after 26 weeks of treatment.

TABLE 5: NEURO-QOL FATIGUE

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQFTG13	I felt exhausted	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG11	I felt that I had no energy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG15	I felt fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG06	I was too tired to do my household chores	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG07	I was too tired to leave the house	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG10	I was frustrated by being too tired to do the things I wanted to do	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG14	I felt tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG02	I had to limit my social activity because I was tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG01	I needed help doing my usual activities because of my fatigue	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG03	I needed to sleep during the day	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG04	I had trouble starting things because I was too tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG05	I had trouble finishing things because I was too tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG08	I was too tired to take a short walk	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG09	I was too tired to eat	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG12	I was so tired that I needed to rest during the day	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG16	I felt weak all over	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG17	I needed help doing my usual activities because of weakness	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG18	I had to limit my social activity because I was physically weak	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG20	I had to force myself to get up and do things because I was physically too weak	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The EUROQOL (EQ-5D) is a reliable and validated survey of health status in 5 areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, completed by the subject. Each area has 3 levels: level 1 (no problems), level 2 (some problems), and level 3 (extreme problems) (*see* Figures 2A and 2B). The EQ VAS records the subject's self-rated health on a vertical, 20 cm visual analogue scale where the endpoints are labeled "Best imaginable health state, marked as 100" and "Worst imaginable health state, marked as 0." The EQ-5D is administered at Day 1, Weeks 4, 8, 12, 16, 20, and 26 or ET (Visits 2, 6, 8, 10, 12, 14, and 17 or ET). A clinically meaningful improvement in a patient's EQ-5D would be reflected as an increase in score after 26 weeks of treatment.

Subjects with increasingly severe MG can suffer from potentially fatal respiratory complications including profound respiratory muscle weakness. Respiratory function is monitored closely for evidence of respiratory failure in MG subjects and ventilator support is recommended in the event of consistent declines in serial measurements of Forced Vital Capacity (FVC) or Negative Inspiratory Force (NIF), loss of upper airway integrity (difficulty handling oral secretions, swallowing, or speaking) or in the setting of emerging respiratory failure. FVC as one of the test items in QMG is performed when QMG is performed. NIF was performed using the NIF Meter.

The MG clinical state is assessed using the MGFA Post-Intervention Status. Change in status categories of Improved, Unchanged, Worse, Exacerbation and Died of MG as well as the Minimal Manifestation (MM) can be assessed.

According to certain embodiments, patients administered eculizumab show a reduced MG-ADL. In certain embodiments, the subjects have an initial MG-ADL score of greater than 6 points. In other embodiments, the subjects have an initial MG-ADL score greater than 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 points. In certain embodiments, after a course of treatment with eculizumab, the MG-ADL score of the subject has been reduced to less than 6 points. In other embodiments, the MG-ADL score has been reduced at least 1 point, at least 2 points, at least 3 points, at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points, at least 10 points, at least 11 points, at least 12 points, at least 13 points, at least 14 points, at least 15 points, at least 16 points, at least 17 points, at least 18 points, at least 19 points, at least 20 points, at least 21 points, at least 22 points, at least 23 points, or at least 24 points after treatment with eculizumab. In certain embodiments, the MG-ADL score of the patient is reduced by at least 1 point after a course of treatment with eculizumab. In other embodiments, the MG-ADL of

the patient is reduced by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 points after a course of treatment with eculizumab.

According to certain embodiments, the course of treatment with eculizumab lasts for 26 weeks. According to other embodiments, the course of treatment lasts for 26-52, 26-78, 26-104, 26-130, 26-156, 26-182, 26-208 weeks, or more. In other embodiments, the course of treatment lasts for greater than 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 78, 104, 130, 156, or 182 weeks. According to other embodiments, the course of treatment lasts for greater than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, or more years. In certain embodiments, the course of treatment lasts for the remainder of the subject's life.

According to certain embodiments, during the course of treatment, one or more symptoms or scores associated with MG improves during the course of treatment and is maintained at the improved level throughout treatment. For example, MG-ADL can improve after 26 weeks of treatment with a therapeutic antibody that specifically binds C5 and then remain at the improved level for the duration of the treatment, which is 52 weeks of treatment with a therapeutic antibody that specifically binds C5. One example of a therapeutic antibody that binds C5 is eculizumab.

In certain embodiments, the first sign of improvement occurs by 26 weeks of treatment with a therapeutic antibody that specifically binds C5. According to other embodiments, the first sign of improvement occurs between weeks 1-26, 26-52, 52-78, 78-104, 104-130, 130-156, 156-182, or 182-208 of treatment with a therapeutic antibody that specifically binds C5. In other embodiments, the first sign of improvement occurs at week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 78, 104, 130, 156, or 182.

According to certain embodiments, the first sign of improvement is maintained for a number of weeks during treatment with a binding protein that specifically binds C5, such as eculizumab or an eculizumab variant such as BNJ441. According to certain embodiments, this number of weeks is at least 26. According to other embodiments, this number of weeks is 1-26, 26-52, 52-78, 78-104, 104-130, 130-156, 156-182, or 182-208. In other embodiments, this number of weeks is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 78, 104, 130, 156, or 182.

According to certain embodiments, eculizumab or other anti-C5 antibodies such as

BNJ441, BNJ421, 7086, and 8110 can be administered to a subject suffering from MG at between 600 and 6000 mg. According to other embodiments, the induction dose of eculizumab or other anti-C5 antibodies such as BNJ441, BNJ421, 7086, and 8110 is between 900 and 1500 mg, 900 and 1200 mg, 900 mg, or 1200 mg. According to other embodiments, the maintenance dose of eculizumab or other anti-C5 antibodies such as BNJ441, BNJ 421, 7086, and 8110 is about 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, 4000, 5000, or 6000 mg.

These doses can be administered once a month, once every two weeks, once a week, twice a week, or daily. According to certain embodiments, the dose is administered once every two weeks or once a week. According to other embodiments, eculizumab is administered to a subject suffering from MG in a multiphase dosing regimen. According to certain embodiments, the multiphase dosing regimen has 2, 3, 4, 6, 7, 8, 9, 10, or more phases. In certain embodiments, each phase provides a higher dose than the phase before it.

In certain embodiments, the eculizumab multiphase dosing regimen has two phases. The first phase is an induction phase. This phase provides a dose of 600, 900, 1200, 1500, or 1800 mg per week. In certain embodiments, this phase lasts for 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks. In other embodiments, this phase lasts between 2 and 6 weeks. In other embodiments, the phase lasts for 5 weeks. According to certain embodiments, the dose given any week is higher than the previous week. In other embodiments, the dose remains the same for a number of weeks and is then increased. In some embodiments, the dose remains the same for the first 1, 2, 3, 4, 5, 6, 7, 8, or 9 weeks and is then increased. In other embodiments, the dose remains the same for the first 4 weeks. According to some embodiments, the eculizumab dose is administered at between 600 and 1200 mg, 800 and 1500 mg, 900 and 1200 mg, 900 and 1100 mg, 900 and 1000 mg, 800 and 1000 mg, 800 and 1100 mg, or 800 and 1200 mg for a number of weeks and is then increased. In one embodiment, the eculizumab dose is administered at about 900 mg on day 1 and is followed by doses of 900 mg on day 7, 900 mg on day 14, 900 mg on day 21, and then is increased to 1200 mg for the fifth dose on day 28, and then 1200 mg is administered every 14 ± 2 days thereafter.

In one particular embodiment, the eculizumab induction phase dosing regimen comprises five administered doses on the following schedule:

900 mg on day 1; 900 mg on day 7 (week 1); 900 mg on day 14 (week 2), 900 mg on day 21 (week 3), and 1200 mg on day 28 (week 4), and then 1200 mg is administered every 14 ± 2 days thereafter. The actual days between each dose may vary during the induction by 1 or

2 days to accommodate unexpected events in the patients' schedule.

According to this embodiment, the second phase of eculizumab dosing is the maintenance phase. The maintenance phase of eculizumab dosing can last for between 6 weeks and the life of the subject. According to other embodiments, the maintenance phase lasts for 26-52, 26-78, 26-104, 26-130, 26-156, 26-182, 26-208 weeks, or more. In other embodiments, the maintenance phase lasts for greater than 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 78, 104, 130, 156, or 182 weeks. According to other embodiments, the maintenance phase lasts for greater than 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80 years, or more years. In certain embodiments, the maintenance phase lasts for the remainder of the subject's life.

In certain embodiments, the eculizumab multiphase dosing regimen includes a third phase. This third phase is used when an MG patient must undergo a rescue procedure to maintain clinical stability and includes administering plasma exchange and/or dosing with IVIg. In this phase after plasma is exchanged a dose of eculizumab is administered to replace the drug lost in plasma exchange. According to certain embodiments, this post-rescue eculizumab dose is between 300 and 1200 mg, 400 and 1500 mg, 500 and 1000 mg, 400 and 800 mg, or 500 and 700 mg. According to certain embodiments, this post-rescue eculizumab dose is about 600 mg. In another embodiment, in this post-rescue or third phase a 600 mg eculizumab dose is administered within 1 hour after completion of plasmapheresis. In another embodiment, in the third phase a 600 mg dose is administered within 2 hours after completion of plasmapheresis. In another embodiment, in the third phase a 600 mg dose is administered within 3 hours after completion of plasmapheresis. In another embodiment, in the third phase a 600 mg dose is administered within 4 hours after completion of plasmapheresis. In another embodiment, in the third phase a 600 mg dose is administered within 5 hours after completion of plasmapheresis. In another embodiment, in the third phase a 600 mg dose is administered within 6 hours after completion of plasmapheresis.

2. Pharmaceutical Compositions

Pharmaceutical compositions comprising eculizumab, either alone or in combination with prophylactic agents, therapeutic agents, and/or pharmaceutically acceptable carriers are provided. The pharmaceutical compositions comprising eculizumab provided herein are for use in, but not limited to, diagnosing, detecting, or monitoring a disorder, in preventing, treating, managing, or ameliorating a disorder or one or more symptoms thereof, and/or in

research. The formulation of pharmaceutical compositions, either alone or in combination with prophylactic agents, therapeutic agents, and/or pharmaceutically acceptable carriers, is known to one skilled in the art.

An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of eculizumab or other anti-C5 antibodies such as BNJ441, BNJ 421, 7086, and 8110 provided herein is 600-5000 mg, for example, 900-2000 mg. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens may be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed methods.

3. Combination Therapy

An anti-C5 antibody provided herein also can also be administered with one or more additional medicaments or therapeutic agents useful in the treatment of MG. For example, the additional agent can be a therapeutic agent art-recognized as being useful to treat myasthenia gravis or condition being treated by the antibody provided herein. The combination can also include more than one additional agent, *e.g.*, two or three additional agents.

The binding agent in various embodiments is administered with an agent that is a protein, a peptide, a carbohydrate, a drug, a small molecule, or a genetic material (*e.g.*, DNA or RNA). In various embodiments, the agent is one or more cholinesterase inhibitors, one or more corticosteroids, and/or one or more immunosuppressive drugs (most commonly azathioprine [AZA], cyclosporin, and/or mycophenolate mofetil [MMF]).

Without limiting the disclosure, a number of embodiments of the disclosure are described below for purpose of illustration.

Item 1: A method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering a therapeutically effective amount of an anti-complement component 5 (C5) antibody or antigen binding fragment thereof to the patient, wherein the patient is administered the anti-C5 antibody or antigen binding fragment thereof for at least 26 weeks.

Item 2: A method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering a therapeutically effective amount of an anti-C5 antibody

or antigen binding fragment thereof to the patient, wherein the anti-C5 antibody or antigen binding fragment thereof is eculizumab or an eculizumab variant, and

wherein the patient is administered eculizumab or eculizumab variant for at least 26 weeks.

Item 3: The method of either items 1 or 2, wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability, and

wherein the patient is administered eculizumab for at least 26 weeks.

Item 4: A method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient:

wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability;

wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg of eculizumab as a fifth induction dose on day 28; and

wherein the patient is administered eculizumab for at least 26 weeks.

Item 5: The method of any one of items 1-4, wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter.

Item 6: The method of any one of items 1-5, wherein the dosing regimen further comprises a third phase.

Item 7: The method of any one of items 1-6, wherein the third phase comprises performing plasmapheresis on the patient and administering eculizumab at a dose of between 300 mg and 1200 mg to the patient within 4 hours of completion of plasmapheresis.

Item 8: The method of any one of items 1-7, wherein the third phase comprises

performing plasmapheresis on the patient and administering eculizumab at a dose of between 600 mg and 900 mg to the patient within 90 minutes of completion of plasmapheresis.

Item 9: The method of any one of items 1-8, wherein the third phase comprises performing plasmapheresis on the patient and administering eculizumab at a dose of 600 mg to the patient within 1 hour of completion of plasmapheresis.

Item 10: The method of any one of items 1-9, wherein the patient experiences a clinically meaningful improvement (reduction) in Myasthenia Gravis Activities of Daily Living (MG-ADL) score after 26 weeks of treatment.

Item 11: The method of any one of items 1-10, wherein the clinically meaningful improvement the patient experiences is at least a 3 point reduction in the patient's MG-ADL score after 26 weeks of treatment.

Item 12: The method of any one of items 1-11, wherein the clinically meaningful improvement the patient experiences is at least a 4 point reduction in the patient's MG-ADL score after 26 weeks of treatment.

Item 13: The method of any one of items 1-12, wherein the patient experiences a clinically meaningful improvement (reduction) in quantitative Myasthenia Gravis score (QMG) after 26 weeks of treatment.

Item 14: The method of any one of items 1-13, wherein the clinically meaningful improvement the patient experiences is at least a 4 point reduction in the patient's QMG score after 26 weeks of treatment.

Item 15: The method of any one of items 1-14, wherein the clinically meaningful improvement the patient experiences is at least a 5 point reduction in the patient's QMG score after 26 weeks of treatment.

Item 16: The method of any one of items 1-15, wherein the patient experiences a clinically meaningful improvement (reduction) in Myasthenia Gravis Composite (MGC) score after 26 weeks of treatment.

Item 17: The method of any one of items 1-16, wherein the clinically meaningful improvement the patient experiences is at least a 6 point reduction in the patient's MGC score after 26 weeks of treatment.

Item 18: The method of any one of items 1-17, wherein the clinically meaningful improvement the patient experiences is at least a 10 point reduction in the patient's MGC score after 26 weeks of treatment.

Item 19: The method of any one of items 1-18, wherein the patient experiences a

clinically meaningful improvement in quality of life as measured by Myasthenia Gravis Quality of Life (MG-QOL-15) score after 26 weeks of treatment.

Item 20: The method of any one of items 1-19, wherein the clinically meaningful improvement the patient experiences is at least a 6 point reduction in the patient's MG-QOL-15 score after 26 weeks of treatment.

Item 21: The method of any one of items 1-20, wherein the clinically meaningful improvement the patient experiences is at least an 11 point reduction in the patient's MG-QOL-15 score after 26 weeks of treatment.

Item 22: The method of any one of items 1-21, wherein the patient experiences a clinically meaningful improvement (reduction) in neuro-fatigue as measured by Neuro-QOL Fatigue score after 26 weeks of treatment.

Items 23: The method of any one of items 1-22, wherein the clinically meaningful improvement the patient experiences is at least an 8 point reduction in the patient's Neuro-QOL score after 26 weeks of treatment.

Item 24: The method of any one of items 1-23, wherein the clinically meaningful improvement the patient experiences is at least a 16 point reduction in the patient's Neuro-QOL score after 26 weeks of treatment.

Item 25: The method of any one of items 1-24, wherein the patient experiences a clinically meaningful improvement (increase) in health status as measured by EQ-5D health status score after 26 weeks of treatment.

Item 26: A method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient:

wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability;

wherein eculizumab is administered using a phased dosing schedule comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg as a fifth dose on day 28;

wherein the patient is administered eculizumab for at least 26 weeks;

wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth

induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter; and

wherein the patient has a clinically meaningful improvement (reduction) in at least two measurements of generalized myasthenia gravis severity selected from the group consisting of MG-ADL, QMG, MGC, MG-QOL, and Neuro-QOL.

Item 27: A method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient:

wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability;

wherein eculizumab is administered using a phased dosing schedule comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg of eculizumab as a fifth induction dose on day 28;

wherein the patient is administered eculizumab for at least 26 weeks;

wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter; and

wherein the patient has a clinically meaningful improvement (reduction) in at least three measurements of generalized myasthenia gravis severity selected from the group consisting of MG-ADL, QMG, MGC, MG-QOL, and Neuro-QOL.

Item 28: The method of any one of items 1-27, wherein the patient has a clinically meaningful improvement (reduction) in at least four measurements of generalized myasthenia gravis severity selected from the group consisting of MG-ADL, QMG, MGC, MG-QOL, and Neuro-QOL.

Item 29: The method of any one of items 1-28, wherein the patient has a clinically meaningful improvement (reduction) in five measurements of generalized myasthenia gravis severity, wherein the five measurements of generalized myasthenia gravis severity are MG-ADL, QMG, MGC, MG-QOL, and Neuro-QOL.

Item 30: A method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient:

wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine

receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability;

wherein eculizumab is administered using a phased dosing schedule comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg as a fifth induction dose on day 28;

wherein the patient is administered eculizumab for at least 26 weeks;

wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter; and

wherein the patient has a clinically meaningful improvement (reduction) in five measurements of generalized myasthenia gravis severity, wherein the five measurements of generalized myasthenia gravis severity are a reduction in MG-ADL of at least 3 points, a reduction in QMG of at least 4 points, a reduction in MGC of at least 6 points, a reduction in MG-QOL of at least 6 points, and a reduction in Neuro-QOL of at least 8 points.

Item 31: The method of any one of items 1-30, wherein the patient has a clinically meaningful improvement (reduction) in five measurements of generalized myasthenia gravis severity, wherein the five measurements of generalized myasthenia gravis severity are a reduction in MG-ADL of at least 4 points, a reduction in QMG of at least 5 points, a reduction in MGC of at least 10 points, a reduction in MG-QOL of at least 11 points, and a reduction in Neuro-QOL of at least 16 points.

Item 32: The method of any one of items 1-31, wherein eculizumab is administered by intravenous infusion.

Item 33: The method of any one of items 1-32, wherein eculizumab is administered subcutaneously.

Item 34: The method of any one of items 1-33, wherein the eculizumab comprises a heavy chain amino acid sequence according to SEQ ID NO: 10 and a light chain amino acid sequence according to SEQ ID NO: 11.

Item 35: The method of any one of items 1-34, wherein the eculizumab is an eculizumab variant comprising a heavy chain amino acid sequence according to SEQ ID NO: 14 and a light chain amino acid sequence according to SEQ ID NO: 11.

Item 36: The method of any one of items 1-35, wherein the eculizumab is an eculizumab variant comprising a heavy chain variable region amino acid sequence according to SEQ ID NO: 12 and a light chain amino acid sequence according to SEQ ID NO: 11.

Item 37: The method of any one of items 1-36, wherein the anti-C5 antibody or antigen binding fragment thereof comprises a heavy chain variable region amino acid sequence according to SEQ ID NO: 27 and a light chain variable region amino acid sequence according to SEQ ID NO: 28.

Item 38: The method of any one of items 1-37, wherein the anti-C5 antibody or antigen binding fragment thereof comprises a heavy chain variable region amino acid sequence according to SEQ ID NO: 35 and a light chain variable region amino acid sequence according to SEQ ID NO: 36.

Item 39: The method of any one of items 1-38, wherein the patient has failed treatment over one year or more with two or more ISTs in sequence or in combination.

Item 40: The method of any one of items 1-39, wherein the patient has failed at least one IST and requires chronic plasma exchange or IVIg to control symptoms of myasthenia gravis.

Item 41: A method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient:

wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and wherein the patient had previously failed treatment with at least two immunosuppressive agents or failed treatment with at least one immunosuppressive agent and required chronic plasma exchange or IVIg, and had an MG-ADL total score $\geq$6 at study entry;

wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg of eculizumab as a fifth induction dose on day 28;

wherein the patient is administered eculizumab for at least 26 weeks;

wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 $\pm$ 2 days thereafter; and

wherein the patient has a clinically meaningful improvement (reduction) in at least two measurements of generalized myasthenia gravis severity selected from the group consisting of MG-ADL, QMG, and MGC.

Item 42: The method of any one of items 1-41, wherein the therapeutically effective amount of eculizumab or eculizumab variant administered to the patient is maintained at a concentration of between 50-100 μg/mL in the patient's serum.

Item 43: The method of any one of items 1-42, wherein the patient experiences a discontinuation in the administration of one or more IST following at least 26 weeks of treatment.

Item 44: The method of any one of items 1-43, wherein the patient experiences a reduction in IST dosing following at least 26 weeks of treatment.

Item 45: The method of any one of items 1-44, wherein the patient experiences a reduction in one or more IST dosing and a discontinuation in one or more IST following at least 26 of treatment.

EXAMPLES

Example 1: Effectiveness of eculizimab in treating myasthenia gravis in human subjects.

The primary objective of this trial is to assess the efficacy of eculizumab as compared with placebo in the treatment of refractory gMG based on the improvement in the MG-specific Activities of Daily Living profile (MG-ADL).

The secondary objectives of this trial include the following:

- Characterize the overall safety and tolerability of eculizumab as compared with placebo in gMG subjects
- Assess the efficacy of eculizumab as compared with placebo by additional efficacy measures including:
  - Quantitative MG (QMG) Score for Disease Severity
  - Myasthenia Gravis Composite (MGC)
  - Improvement in primary symptoms that are most clinically meaningful to the subjects
  - MG-ADL subcategories for bulbar, respiratory, limb and ocular
- Characterize the effect of eculizumab as compared with placebo on Quality of life measures
- Describe the PK and PD of eculizumab in gMG subjects.

1. Investigational Plan

1.1. Overall Trial Design and Plan

Described herein is a randomized, double-blind, parallel-group, placebo-controlled, multicenter (~100 sites in North America, South America, Europe, Asian Pacific) approximately two year trial to evaluate the safety and efficacy of eculizumab for the treatment in subjects with refractory gMG. Approximately 92 eligible subjects are randomized on Day 1 on a 1:1 ratio to one of two treatment arms (1) eculizumab infusion or (2) placebo infusion. Subjects may continue to receive stable dose/type of immunosuppressive therapy (IST), but no new ISTs and no increase in IST dosage are permitted during the trial. There are 3 periods in this study: Screening Period, Study Period, and Follow-up Period (for subjects who withdraw from this trial or who do not enter the extension trial). *See* Figure 1. The overall trial duration for an individual subject is estimated to take up to 38 weeks including enrollment and Follow-up. Subjects may be provided the opportunity to participate in an extension trial (separate protocol) to receive eculizumab after completion of this trial. A schedule of assessments for the screening, study and follow-up period is provided in Table 6.

1.1.1. Screening Period (2-4 Weeks)

At the screening visit, after obtaining the informed consent from the subject, the subject is screened for trial eligibility through medical history review, demographic data, and laboratory assessments. The medical history review includes confirmation of MG diagnosis as defined in the inclusion criteria of this protocol, history of previous treatment / therapies for MG, *e.g.*, thymectomy, IST including corticosteroids, IVIg and plasma exchange, history of MG exacerbation or crisis including the duration of each exacerbation/crisis, the medication taken at the time of each exacerbation/crisis and the treatment for each exacerbation/ crisis.

If all inclusion criteria and none of the exclusion criteria are met, subjects are vaccinated against *N. meningitidis*, if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer or vaccinate according to current medical/country guidelines. Subjects must be vaccinated at least 14 days prior to receiving the first dose of study medication or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination. *See* Figure 3.

Use of cholinesterase inhibitor and supportive IST are allowed during the trial under certain restrictions (*see* Concomitant Medications, below). The washout period for IVIg is 4

weeks prior to randomization. The washout period for PE is also 4 weeks prior to randomization. If a subject experiences an MG Crisis during the Screening Period, the sponsor must be notified. Following discussion with the sponsor, a decision is made about whether the subject may continue in the trial, be withdrawn and possibly, re-screened at a later date.

TABLE 6: TRIAL DESIGN AND SCHEDULE OF ASSESSMENTS (STUDY PERIOD)

Period /Phase	Screening	Induction					Maintenance											^ Clinical Deterioration	++ UNS Visit	Post-Treatment Follow-up
Trial Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/ ET***			
Trial Weeks	**2 – 4 Weeks**	**D1**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**			**+W8**
Informed Consent	X																			
Medical History	X																			
MG History [1]	X																			
MGFA Clinical Classification	X																			
Weight	X																X			
Height	X																			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Exam	X																			
12-Lead ECG	X																X			
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
MG Therapy Status	X	X															X			
Adverse Event		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
MG-QOL 15	X	X				X		X		X		X		X			X			X
Neuro-QOL Fatigue		X				X		X		X		X		X			X			
EQ-5D		X				X		X		X		X		X			X			
MG-ADL [2]	X	X	X	X	X	X		X		X		X		X			X	X		X
QMG [3]	X	X	X	X	X	X		X		X		X		X			X	X		X
NIF [3]	X	X	X	X	X	X		X		X		X		X			X	X		X
MGC [3]	X	X	X	X	X	X		X		X		X		X			X	X		X
MGFA PIS [4]						X				X							X			X
C-SSRS		X								X							X			
AChR Ab	X									X							X	X		
Clinical Lab Tests [5]	X	X				X		X		X		X		X			X	X		
Pregnancy Test [6]	X	X															X			
PK/PD, Free C5 [7]		B/ P	T/P			T/P		T/P		T/P				T/P			T/P	X		
HAHA [7]		B				X				X							X			
Medically Indicated Tests																		X		

Period /Phase	Screening	Induction					Maintenance											^ Clinical Deterioration	++ UNS Visit	Post-Treatment Follow-up
Trial Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/ ET***			
Trial Weeks	**2 – 4 Weeks**	**D1**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**			**+W8**
N. meningitidis Vaccination [8]	X																			
Patient Safety Information Card		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Randomization [9]		X																		
IP Infusion [10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [10]		

Abbreviations:

AChR Ab=Acetylcholine receptor antibody; B=Baseline sample; C5=Complement protein 5; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=Electrocardiogram; ICU=Intensive Care Unit; HAHA = human anti-human antibody; ; IP = investigational product; MG=Myasthenia Gravis; MGC = MG Composite Score; MG-ADL = MG Activity of Daily Living (MG-ADL) Profile; MGFA = Myasthenia Gravis Foundation of America; MGFA PIS = MGFA Post-Intervention Status; NIF = negative inspiratory force; P = peak sample; PK/PD=Pharmacokinetics/Pharmacodynamics QMG = Quantitative MG (QMG) Score for Disease Severity; QOL=Quality of Life; T = trough sample

1.1.2. Randomization

All subjects who are vaccinated, and continue to meet the MG-ADL entry criteria, *i.e.*, MG-ADL total score ≥ 6 at Randomization (Day 1), and have been cleared for randomization by their respective Principal Investigator (PI), will be randomized on Day 1 on a 1:1 basis to the Eculizumab Arm or the Placebo Arm. The randomization stratification is based on the assessment of clinical classification by the Myasthenia Gravis Foundation of America (MGFA) (*see* Table 7) performed at the Screening Visit according to the following 4 groupings:

a. MGFA Class IIa and IIIa
b. MGFA Class IVa
c. MGFA Class IIb and IIIb, and
d. MGFA Class IVb

1.1.3. Study Period (26 Weeks)

Subjects receive IP, either eculizumab or placebo, according to the randomization and the regimen described in the Investigational Product and Administration, described below. The treatment duration for each subject is 26-weeks. Subjects must be informed of potential signs and symptoms of MG crisis and instructed to contact the Investigator as soon as possible at onset of symptom. Every effort is made for the subject reporting Clinical Deterioration to be evaluated as soon as possible and within 48 hours of notification of the Investigator of the symptom onset. At the evaluation visit, the Investigator or his/her designee performs the assessments as specified by this protocol. The Investigator determines whether or not the subject meets the definition of Clinical Deterioration as defined by this protocol and treats the subject accordingly.

TABLE 7: MGFA CLINICAL CLASSIFICATION

Class	Clinical signs
I	Any ocular muscle weakness. May have weakness of eye closure. All other muscle strength is normal.
II	Mild weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IIa	Predominantly affecting limb or axial muscles or both. May also have lesser involvement of oropharyngeal muscles.
IIb	Predominantly affecting oropharyngeal or respiratory muscles or both. May also have lesser or equal involvement of limb or axial muscles or both.
III	Moderate weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IIIa	Predominantly affecting limb or axial muscles or both. May also have lesser involvement of oropharyngeal muscles.
IIIb	Predominantly affecting oropharyngeal or respiratory muscles or both. May also have lesser or equal involvement of limb or axial muscles or both.
IV	Severe weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IVa	Predominantly affecting limb and/or axial muscles. May also have lesser involvement of oropharyngeal muscles.
IVb	Predominantly affecting oropharyngeal or respiratory muscles or both. May also have lesser or equal involvement of limb or axial muscles or both.
V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management The use of a feeding tube without intubation places the patient in class IVb.

After completing the 26-week Study Period, subjects may be provided an opportunity to enter an extension trial (separate protocol) to receive open-label eculizumab. The visit interval between this trial and the extension trial is 2 weeks from the last of IP administration (Visit 17) so there is no interruption in IP dosing. Subjects entering the extension trial undergo a blinded eculizumab induction phase similar to the induction in this trial in order to maintain the blinded treatment assignment of this trial. If a subject withdraws from this trial at any time after receiving any amount of IP or does not wish to enter the extension trial after completion of this trial, the subject is required to complete the Follow-up Visit for safety measures.

1.1.4. Follow-up Period (8 Weeks Post-Treatment)

If a subject withdraws or is discontinued from this trial at any time after receiving any amount of IP or does not wish to enter the extension trial after completion of this trial, the subject will be required to complete the Follow-up Visit for safety measures 8 weeks after the last IP dose administration. If a subject is discontinued due to an AE, the event will be followed until it is resolved or in the opinion of the PI is medically stable.

1.2. Standard Protocol Definitions

Abbreviations and definitions for the study and follow-up period are provided in Table 8.

TABLE 8: LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
Ab	Antibody
AChR	Acetylcholine receptor
AE	Adverse event
aHUS	Atypical hemolytic uremic syndrome
ANCOVA	Analysis of covariance
AZA	Azathioprine
BP	Blood Pressure
C5	Complement protein 5
CMAX	Maximal concentration
CMIN	Minimal concentration
eCRF	Electronic Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
EDC	Electronic Data Capture
EIU	Exposure in-utero
EOI	Event of Interest
EOS	End of Study
EQ-5D	EuroQoL
ET	Early Termination
EU	European Union
FAS	Full Analysis Set
FVC	Forced Vital Capacity
GCP	Good Clinical Practices
gMG	Generalized Myasthenia Gravis
HAHA	Human Anti-human Antibody
HCG	human chorionic gonadotropin
HR	Heart Rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IVIg	Intravenous Immunoglobulin G
IP	Investigational Product
IRB	Institutional Review Board
IST	Immunosuppressant Therapy

IV	Intravenous
IVIg	Intravenous immunoglobulin
IXRS	Interactive voice or web response system
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia Gravis
MG-ADL	MG activity of daily living profile
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MM	Minimal manifestation
MMF	Mycophenolate Mofetil
MMT	Manual Muscle Test
MTX	Methotrexate
MuSK	Muscle-specific tyrosine kinase
NIF	Negative inspiratory force
NMJ	Neuromuscular junction
oMG	Ocular Myasthenia Gravis
PD	Pharmacodynamics
PE	Plasmapheresis or Plasma Exchange
PI	Principal Investigator
PIS	Post-Intervention Status
PK	Pharmacokinetics
PNH	Paroxysmal Nocturnal Hemoglobinuria
PP	Per-Protocol Population
QOL	Quality Of Life
QMG	Quantitative Myasthenia Gravis
RR	Respiration Rate
RSI	Reference Safety Informatoion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFEMG	single-fiber electromyography
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Events
TESAE	Treatment Emergent SAE
US	United States
VAS	Visual Analog Scale
WHODrug	World Health Organization Drug Dictionary

1.2.1. Clinical Deterioration

For this protocol, Clinical Deterioration is defined as follows:

- Subjects who experience an MG Crisis, which is defined as weakness from MG that is severe enough to necessitate intubation or to delay extubation following surgery. The respiratory failure is due to weakness of respiratory muscles. Severe bulbar (oropharyngeal) muscle weakness often accompanies the respiratory muscle weakness, or may be the predominant feature in some subjects; or,
- Significant symptomatic worsening to a score of 3 or a 2-point worsening on any one of the individual MG-ADL items other than double vision or eyelid droop; or,
- Subjects for whom the treating physician believes that the subject's health is

in jeopardy if rescue therapy is not given (*e.g.*, emergency situations).

1.2.2. Clinical Evaluation

The Clinical Evaluators are study staff that have been trained and certified in administering the MG-ADL, QMG and MGC. The Clinical Evaluator may be a neurologist, physical therapist or other study team member delegated by the PI. Clinical Evaluator training and certification for this protocol will take place either at the Investigator's meeting or via the sponsor's designated on-line training portal.1.2.3.

RESPONSIBILITIES FOR MG ASSESSMENTS

Responsibilities for MG assessments are listed in Table 9. Throughout the trial, MG assessments should be performed at approximately the same time of day by a properly trained evaluator, preferably the same evaluator.

TABLE 9: MG ASSESSMENTS (RESPONSIBILITIES)

Assessment	**Evaluator**
MG-ADL	Clinical Evaluator
QMG including FVC	Clinical Evaluator
NIF	Clinical Evaluator
MGC	Clinical Evaluator
MGC (MMT Components)	PI or Neurologist
MGFA-PIS	PI or Neurologist
MGFA Classification	PI or Neurologist

Abbreviations: FVC = forced vital capacity; MG-ADL = Myasthenia Gravis Activity of Daily Living Profile; MGC = Myasthenia Gravis Composite; MGFA = Myasthenia Gravis Foundation of America; MGFA-PIS = Myasthenia Gravis Foundation of America Post Intervention Status; MMT = manual muscle test; NIF = negative inspiratory force; PI = Principal Investigator; QMG = Quantitative MG

1.4. Trial Visit Procedures

1.4.1. Screening Visit

(Days -28 to -14 prior to Baseline [Visit 2/Day 1])

After obtaining a signed informed consent form, the following tests and evaluations are performed within 2-4 weeks prior to randomization at the Baseline Visit (Visit 2/Day 1) to determine subject eligibility for participation in this trial:

- Review inclusion and exclusion criteria; Register the subject in the IXRS system to get the subject identification number in the study and trigger drug shipment if necessary; Record medical history and demographics; Record MGFA Clinical Classification
- Record MG history:
  a. Confirm MG diagnosis as defined by the protocol inclusion criterion #2

b. Record the initial MG clinical presentation (*i.e.*, oMG or gMG). If the initial clinical presentation was oMG, record the time (date) to onset of gMG

c. Record the maximum MGFA classification since diagnosis, if available

d. Record whether the subject ever required ventilatory support since the diagnosis

e. Record the number of hospitalizations, including number of ICU stays (days) and any ventilatory support associated with the hospitalization within the last 2 years prior to screening

f. Record number and duration of all previous MG exacerbations or record number and duration of all previous MG exacerbations or crisis, the medication / therapy taken at the time of each exacerbation or crisis, and medication / therapy use for treatment of each exacerbation or crisis, if applicable.

- Record MG Therapy Status (*see* Table 9)
- Measure body weight and height
- Measure vital signs, including assessments of systolic and diastolic blood pressure (BP), temperature, respiration rate (RR) and heart rate (HR)
- Complete physical examination including assessments of the following organ/body systems: skin, head, ears, eyes, nose, throat, neck, lymph nodes, chest, heart, abdomen, extremities, musculoskeletal, and general neurologic examination.
- Perform a 12-Lead ECG
- Record concomitant medications, including prior IST, IVIg, and/or PE for MG from the time of diagnosis up to screening and all other concomitant medications within 30 days prior to the Screening Visit.
- Administer MG-ADL by a properly trained evaluator. The recall period is the preceding 7 days.
- Administer clinical assessments QMG, NIF, and MGC; these should be performed at approximately the same time of day by a properly trained evaluator. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.

- Administer MG-QOL15 questionnaire to evaluate quality of life.
- Obtain blood sample for AChR Abs test.
- Obtain blood samples for laboratory tests (chemistry and hematology) (*see* Table 6)
- Obtain pregnancy test (serum) for all women of childbearing potential. Note: if the subject is taking/using contraceptive medication/device, please be sure to record the medication or device on the appropriate electronic case report form (eCRF) pages (concomitant medication or procedure).
- If all inclusion criteria and none of the exclusion criteria are met, subjects will be vaccinated against *N. meningitides,* if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer or according to current medical/country guidelines. Subjects must be vaccinated at least 14 days prior to receiving the first dose of study medication or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination.
- If a subject experiences an MG Crisis during the Screening Period, the sponsor should be notified. Following discussion with the sponsor, a decision will be made about whether the subject may continue in the trial, be withdrawn and possibly, re-screened at a later date.

1.4.2. Study Period

Visit intervals during Induction Phase (Visits 2, 3, 4, 5 and 6) are weekly (every 7 ± 2 days after the last visit). Visit intervals during the Maintenance Phase (Visits 7 – 17) are every 2 weeks (every 14 days ± 2 days since the last visit). Subjects who fail to return for a scheduled visit must be contacted by the site study staffs to determine the reason for missing the appointment. Subjects are strongly encouraged to return to the investigational site for evaluation if Clinical Deterioration or an AE is suspected to have occurred. In the exceptional circumstance where a subject cannot or does not come to the study site for examination, then the subject will be instructed to see his or her local neurologist or physician. In this event, the investigational site obtains relevant medical records as documentation from the local physician's examination, and enters relevant data in the eCRF as appropriate.

TABLE 9: MGFA MG THERAPY STATUS

NT	No therapy
SPT	Status postthymectomy (record type of resection)
CH	Cholinesterase inhibitors
PR	Prednisone
IM	Immunosuppression therapy other than prednisone (define)
PE(a)	Plasma exchange therapy, acute (for exacerbations or preoperatively)
PE(c)	Plasma exchange therapy, chronic (used on a regular basis)
IG(a)	IVIg therapy, acute (for exacerbations or preoperatively)
IG(c)	IVIg therapy, chronic (used on a regular basis)
OT	Other forms of therapy (define)

As it is vital to obtain information on any subject's missing visit to assure the missing appointment was not due to a clinical deterioration or an AE, every effort must be made to undertake protocol-specified follow-up procedures (*see* Table 6). Follow-up due diligence documentation consists of 3 phone calls followed by 1 registered letter to the subject's last known address. The study period is summarized in Table 6 and Figure 6.

1.4.2.1. Induction Phase (Baseline [Visit 2/Day 1] until Visit 6 [Week 4])

1.4.2.1.1. Baseline (Visit 2/Day 1)

Once all of the eligibility criteria have been confirmed by the PI, the subject is randomized on Day 1. The following tests and procedures are completed at the Baseline Visit (Visit 2/Day 1):

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR and HR
- Record MG Therapy Status (*see* Table 9)
- Record any new medications or changes to concomitant medications
- Evaluate and record AEs since the previous visit
- Administer questionnaires to evaluate quality of life (MG-QOL 15, Neuro-QOL Fatigue, and EuroQoL [EQ-5D])
- Administer MG-ADL by a properly trained evaluator, preferably the same evaluator, throughout the trial. The recall period is the preceding 7 days. If the

number of days since the last visit was <7, the recall period is since the last visit.

- Administer clinical assessments QMG, NIF, and MGC; these should be performed at approximately the same time of day by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Perform Columbia-Suicide Severity Rating Scale (C-SSRS)
- Obtain blood samples for clinical laboratory tests (chemistry and hematology)
- Obtain pregnancy test (serum) for all women of childbearing potential.
- Collect baseline blood samples for PK, PD, free C5, and HAHA assays 5-90 minutes before the infusion of IP.
- Instruct the subject on the signs and symptoms of *N.* meningitis. Provide the Patient Safety Information Card describing the IP and emergency contact information to the subject prior to the first dose of IP.
- Randomize the subject using the IXRS.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in Section 4.5, and observe subjects for 1 hour after the end of the IP infusion.
- Collect peak blood samples for PK, PD, and free C5 assays at least 60 minutes after completion of the IP infusion.

1.4.2.1.2. Visits 3-5 (Weeks 1-3)

The following tests and procedures are completed:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR
- Record any new medications or changes to concomitant medications
- Evaluate and record any new AEs or changes in AEs since the previous visit.
- Administer MG-ADL by a properly trained evaluator, preferably the same evaluator, throughout the trial. The recall period is the preceding 7 days. If the number of days since the last visit was <7, the recall period is since the last visit.
- Administer clinical assessments QMG, NIF, and MGC; these should be performed at approximately the same time of day by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and

MGC tests.

- At Visit 3 (Week 1) only, collect trough (before IP infusion) blood samples for PK, PD, and free C5 assays. Trough blood samples are to be taken 5-90 minutes before the IP infusion.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Obtain study drug kit assignation through the IXRS.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in Section 4.5, and observe subjects for 1 hour after the end of the IP infusion.
- At Visit 3 (Week 1) only, collect peak (after IP infusion) blood samples for PK, PD, and free C5 assays. Peak blood samples are to be taken at least 60 minutes after the completion of the IP infusion.

1.4.2.1.3. Visit 6 (Week 4)

The following tests and procedures are completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR
- Record any new medications or changes to concomitant medications
- Evaluate and record any new AEs or changes in AEs since the previous visit
- Administer questionnaires to evaluate quality of life (MG-QOL 15, Neuro-QOL Fatigue, and EQ-5D)
- Administer MG-ADL by a properly trained evaluator, preferably the same evaluator, throughout the trial. The recall period is the preceding 7 days. If the number of days since the last visit was <7, the recall period is since the last visit.
- Administer clinical assessments QMG, NIF, and MGC; these should be performed at approximately the same time of day by an appropriately trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Assess change from baseline in the MGFA Post-Intervention Status (*see* Table 10).
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Collect trough blood samples for PK, PD, free C5, and HAHA assays 5-90 minutes before the infusion of IP.

- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Obtain study drug kit assignation through the IXRS.
- Administer the IP infusion over approximately 35 minutes according to the regimen described in Section 4.5, and observe subjects for 1 hour after the end of the IP infusion.
- Collect peak blood samples for PK, PD, and free C5 assays at least 60 minutes after completion of the IP infusion.

1.4.2.2. Maintenance Phase (Visit 7 [Week 6] until End of Study Period Visit 17 [Week 26] or Early Termination of Visit)

During the Maintenance Phase, subjects return for infusions of IP every 2 weeks (14 ± 2 days), according to the regimen described in Section 4.5. The following tests and procedures are completed at every visit beginning at Visit 7 (Week 6) and continuing until the End of Study (EOS), Visit 17 (Week 26) or at Early Termination (ET):

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR
- Record any new medications or changes to concomitant medications
- Evaluate and record any new AEs or changes in AEs since the previous visit.
- Ensure that the subject has the Patient Safety Information Card that describes the IP and emergency contact information.
- Administer the IP and observe subjects for 1 hour after the end of the IP infusion. IP will be administered **after** completion of other tests and procedures, excluding the peak blood sampling for PK/PD and free C5 assay.

At Visit 8 (Week 8), Visit 10 (Week 12), Visit 12 (Week 16), Visit 14 (Week 20), and until the EOS, Visit 17 (Week 26) or at ET, the following procedures are also completed, in addition to the 5 preceding procedures listed for the maintenance phase:

- Administer questionnaires to evaluate quality of life (MG-QOL 15, Neuro-QOL Fatigue, and EQ-5D)
- Administer MG-ADL by a properly trained evaluator, preferable the same evaluator, throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG, NIF, and MGC; these should be performed at approximately the same time of day by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase

inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.

- Perform C-SSRS only at Visit 10 (Week 12) and Visit 17 (Week 26)/ET. The blood sample for the HAHA assay is to be collected 5-90 minutes before the infusion of IP.
- Obtain blood sample for clinical laboratory tests (chemistry and hematology).
- Obtain blood sample for the AChR Abs test and HAHA assay only at Visit 10 (Week 12) and Visit 17 (Week 26)/ET.
- Collect trough blood samples for PK, PD, and free C5 assays 5-90 minutes before the infusion of IP only at Visits 8, 10, 14 and 17/ET (Weeks 8, 12, 20, and 26).
- Collect peak blood samples for PK, PD, and free C5 assays at least 60 minutes after completion of the IP infusion only at Visits 8, 10, 14 and 17/ET (Weeks 8, 12, 20, and 26).
- Measure body weight only at Visit 17 (Week 26)/ET.
- Perform a 12-Lead ECG only at Visit 17 (Week 26)/ET.
- Record MG Therapy Status (*see* Table 9) only at Visit 17 (Week 26)/ET.
- Obtain pregnancy test must for all women of childbearing potential at Visit 17 (Week 26)/ET.
- Assess change from baseline in the MGFA Post-Intervention Status only at Visit 10 (Week 12) and Visit 17 (Week 26)/ET.

1.4.2.3. Visits for MG Crisis or Clinical Deterioration

The evaluation visit for an MG crisis or Clinical Deterioration must be performed as soon as possible, within 48 hours of notification of the Investigator of the symptom onset. Additional evaluation visits can be scheduled at the discretion of the investigator. The following tests and procedures are completed at this visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR
- Record any new medications or changes to concomitant medications, including all treatments for MG
- Evaluate and record any new AEs or changes in AEs since the previous visit
- Administer MG-ADL by a properly trained evaluator, preferably the same

evaluator, throughout the trial. The recall period is the preceding 7 days or since the last visit whichever occurs earlier.

- Administer clinical assessments QMG, NIF, and MGC; these should be performed at approximately the same time of day by a properly trained evaluator, preferably the same evaluator, throughout the trial.
- Collect blood sample for the AChR Abs test
- Collect blood samples for clinical laboratory tests (chemistry and hematology)
- If medically indicated for evaluation of Clinical Deterioration, additional tests may be performed at the discretion of the Investigator.
- PK, PD sampling at or during crisis or deterioration Visit:
  - Collect one blood sample for PK, PD, and free C5 assays if no IP is administered.
  - If IP is administered at the MG Crisis evaluation visit or at the visit for Clinical Deterioration, according to the protocol schedule, collect two blood samples, trough and peak, at [1] 5-90 minutes before the IP infusion and [2] at least 60 minutes after completion of the IP infusion.
  - If the subject receives PE at the time of a crisis or Clinical Deterioration, a supplemental dose of IP will be administered. Collect three blood samples for PK, PD, and free C5 at [1] 5-90 minutes before PE, [2] 60 minutes after PE and before IP infusion, and [3] at least 60 minutes after completion of the IP infusion.
- IP administration:
  - Subject will continue IP administration in accordance with protocol specified IP administration schedule.
  - If the crisis or Clinical Deterioration Visit coincides with a regular visit per protocol, subject will receive the regular scheduled IP administration per protocol schedule.
  - If subjects undergo PE, a supplemental dose (2 vials IP) must be administered within 60 minutes after each PE session. If the subject is scheduled to receive the protocol-scheduled dose on the day of a PE session, then the scheduled dose should be administered within 60 minutes after the end of the PE.

1.4.2.4 Unscheduled Visit

Additional (Unscheduled) visits outside the specified visits are permitted at the discretion of the Investigator. Procedures, tests, and assessments are performed at the

discretion of the Investigator. If an Unscheduled Visit is performed, any tests, procedures, or assessments performed at the Unscheduled Visits must be recorded on the eCRFs.

1.4.3. Safety Follow-Up Period (Post-Treatment +Week 4) Safety Follow-Up Period (Post-Treatment +Week 8)

If a subject withdraws from the trial at any time during the Study Period after receiving any amount of IP (eculizumab or placebo) or does not wish to enter the extension trial after completion of this trial, a follow up visit for safety assessment is required at 4 weeks after the last dose of IP. The following tests and procedures will be completed at the safety follow-up visit:

- Measure vital signs, including assessments of systolic and diastolic BP, temperature, RR, and HR
- Record any new medications or changes to concomitant medications
- Evaluate and record any new AEs or changes in AEs since the previous visit.
- Administer MG-QOL15
- Administer MG-ADL by a properly trained evaluator, preferably the same evaluator, throughout the trial. The recall period is the preceding 7 days.
- Administer clinical assessments QMG, NIF, and MGC; these should be performed at approximately the same time of day by a properly trained evaluator, preferably the same evaluator, throughout the trial. If the subject is taking a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG and MGC tests.
- Assess change from baseline in MGFA Post-Intervention Status (*see* Table 10).

TABLE 10: MGFA POST-INTERVENTION STATUS

Complete stable remission (CSR)	The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacological remission (PR)	The same criteria as for CSR, except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal manifestations (MM)	The patient has no symptoms of functional limitations from MG, but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
MM-0	The patient has received no MG treatment for at least 1 year.
MM-1	The patient continues to receive some form of immunosuppression, but no cholinesterase inhibitors or other symptomatic therapy.
MM-2	The patient has received only low-dose cholinesterase inhibitors (<120 mg pyridostigmine/day) for at least 1 year.
MM-3	The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.
Change in Status	
Improved (I)	A substantial decrease in pretreatment clinical manifestations or a sustained substantial reduction in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific decrease in QMG score.
Unchanged (U)	No substantial change in pretreatment clinical manifestations or reduction in MG medications as defined in the protocol. In prospective studies, this should be defined in terms of a maximum change in QMG score.
Worse (W)	A substantial increase in pretreatment clinical manifestations or a substantial increase in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific increase in QMG score.
Exacerbation (E)	Patients who have fulfilled criteria of CSR, PR, or MM, but subsequently developed clinical findings greater than permitted by these criteria.
Died of MG (D of MG)	Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy. List the cause (see Morbidity and Mortality data).

If a subject is discontinued due to an AE, the AE will be followed until it is resolved or, in the opinion of the PI, is determined medically stable.

1.5. Number of Subjects

Approximately 92 subjects with refractory gMG are randomized in a 1:1 (eculizumab: placebo) ratio at approximately 100 centers. Randomization is across centers and is stratified based on MGFA clinical classifications (Class a vs. Class b and Classes II and III vs. Class IV) (*see* Table 7).

1.6. Treatment Assignment

Approximately 92 subjects with refractory gMG are randomized, 46 subjects to eculizumab and 46 subjects to placebo. All patients will remain on assigned double-blind treatment until the EOS/ET visit. Randomized subjects who discontinue after initiation of study treatment are not being replaced. Assignment will be performed through the IXRS at each visit.

2. Selection and Withdrawal of Subjects

2.1. Subject Inclusion Criteria

1. Male or female subjects ≥18 years old
2. Diagnosis of MG must be made by the following tests:
   - Positive serologic test for anti-AChR Abs as confirmed at screening, and
   - One of the following:

   a. History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography (SFEMG) or repetitive nerve stimulation, or

   b. History of positive anticholinesterase test, *e.g.*, edrophonium chloride test, or c. Subject has demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating physician.
3. MGFA Clinical Classification Class II to IV at screening.
4. MG-ADL total score must be ≥6 at screening and Randomization (Day 1)
5. Subjects who have
   a. Failed treatment over one year or more with 2 or more ISTs* (either in combination or as mono-therapy), *i.e.*, continue to have impairment ADLs (persistent weakness, experience crisis, or unable to tolerate IST) despite ISTs. Or,

b. Failed at least one IST and require chronic plasma exchange or IVIg to control symptoms, *i.e.*, subjects who require PE or IVIg on a regular basis for the management of muscle weakness at least every 3 months over last 12 months.

* Immunosuppressant's include, but are not limited to, corticosteroids AZA, MMF, methotrexate (MTX), cyclosporine, tacrolimus, or cyclophosphamide.

6. If subjects who enter the study are receiving AZA they must have been on AZA for ≥6 months and have been on a stable dose for ≥2 months prior to screening.
7. If subjects who enter the study are receiving other ISTs, *i.e.*, MMF, MTX, cyclosporine, tacrolimus, or cyclophosphamide, they must have been on the IST for ≥3 months and have been on a stable dose for ≥1 month prior to screening.
8. If subjects who enter the study are receiving oral corticosteroids, they must have been on a stable dose for ≥ 4 weeks (28 days) prior to screening.
9. If subjects who enter the study are receiving a cholinesterase inhibitor they must have been on a stable dose for ≥2 weeks prior to screening.
10. Female subjects of child-bearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG]). All subjects must practice an effective, reliable and medically approved contraceptive regimen during the study and for up to 5 months following discontinuation of treatment.
11. Subject must give written informed consent.
12. Subject must be able and willing to comply with study procedures.

2.2. Subject Exclusion Criteria

1. History of thymoma or other neoplasms of thymus.
2. History of thymectomy within 12 months prior to screening.
3. Weakness only affecting ocular or peri-ocular muscles (MGFA Class I).
4. MG crisis at screening (MGFA Class V)
5. Pregnancy or lactation.
6. Any systemic bacterial or other infection, which is clinically significant in the opinion of the Investigator and has not been treated with appropriate antibiotics
7. Unresolved meningococcal infection.
8. Use of IVIg within 4 weeks prior to Randomization (Day 1).
9. Use of PE within 4 weeks prior to Randomization (Day 1).
10. Use of rituximab within 6 months prior to screening.

11. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedures within 30 days prior to screening.
12. Subjects who have received previous treatment with eculizumab.
13. Hypersensitivity to murine proteins or to one of the excipients of eculizumab.
14. Any medical condition that, in the opinion of the Investigator, might interfere with the subject's participation in the study, poses any added risk for the subject, or confounds the assessment of the subjects.

2.3. Subject Withdrawal Criteria

2.3.1. Withdrawal of Subjects from the Trial

Subjects are allowed to withdraw consent at any time. Every effort should be made to ensure subjects are willing to comply with trial participation prior to conducting the screening procedures and the subjects should be fully informed of the restrictions related to the change of concomitant medications during the trial. Investigators may choose to discontinue a subject's treatment because of AEs, as well as conditions or illnesses that preclude compliance with the protocol from the standpoint of the subject's safety or well-being. The study staff should notify the Sponsor and their site monitor of all trial withdrawals as soon as possible.

Reproduction and development studies with eculizumab have not been performed; therefore, eculizumab should not be administered to pregnant women. At the time of the last follow-up visit, all subjects of childbearing potential must continue to use adequate contraception for up to 5 months following discontinuation of eculizumab treatment. If a subject becomes pregnant, the IP must be immediately discontinued and the Sponsor must be notified. Each pregnancy will be followed to term and the Sponsor notified regarding the outcome.

2.3.2. Handling of Withdrawals

When a subject withdraws or is withdrawn from the trial, the Investigator shall record the withdrawal reason(s). Whenever possible, all subjects who prematurely withdraw from the trial will undergo all assessments at the ET visit for safety as per the Schedule of Assessments (Table 6). A follow-up visit for safety assessment is required at 8 weeks after the last dose of IP administration (Table 6).

If a subject is discontinued due to an AE, the event will be followed until it is resolved or in the opinion of the PI the subject is determined to be medically stable. Every effort will be made to undertake protocol-specified safety follow-up procedures.

Subjects who fail to return for final assessments will be contacted by the site study staffs in an attempt to have them comply with the protocol. As it is vital to obtain follow-up data on any subject withdrawn because of an AE or SAE, follow-up due diligence documentation will consist of 3 phone calls followed by 1 registered letter to the subject's last known address. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures.

2.3.3. Sponsor's Termination of Trial

Alexion Pharmaceuticals, Inc. or a regulatory authority may discontinue the trial at any time for any reason including, for example, clinical or administrative reasons.

2.3.4. End of Trial Definition

The end of trial is defined as the last visit completed by the last patient.

3. Treatment of Subjects

3.1. Description of Investigational Product

Eculizumab (600 mg, 900 mg or 1200 mg) or matching placebo is administered intravenously over approximately 35 minutes according to the regimen shown in Table 11.

TABLE 11: TRIAL DOSE REGIMEN

Dose Period	Frequency of Investigational Product Administration	Visits	# of Vials	Equivalent Eculizumab Dose
Induction Phase	Weekly (every 7 ± 2 days)	2-5	3	900 mg
		6	4	1200 mg
Maintenance Phase	Every 2 weeks (14 ± 2 days) from the fifth dose onward	7 - 17	4	1200 mg
Supplement Doses*	If PE is given due to a Clinical Deterioration, administer within 60 minutes after the end of each PE session as described below*.		2	600 mg

Induction Phase

Eculizumab or placebo: 3 vials of IP (equivalent to 900 mg of eculizumab) weekly for 4 weeks (every 7 days ± 2 days) followed by 4 vials of IP (equivalent to 1200 mg of eculizumab) one week later for the fifth dose (Visit 6/Week 4).

Maintenance Phase

Eculizumab or placebo: 4 vials of IP (equivalent to 1200 mg of eculizumab) every 2

weeks (14 days ± 2 days)

***Supplemental Doses**

If PE is administered due to a Clinical Deterioration (as defined by this protocol), supplemental IP (2 vials, equivalent to 600 mg of eculizumab or matching placebo) will be administered within 60 minutes after the end of each PE session. If PE is administered on a day of regularly scheduled IP administration, subjects will receive the regularly scheduled number of vials (3 vials on Visits 2 - 4; 4 vials on all other visits) within 60 minutes after each PE session.

3.2. Concomitant Medications

3.2.1. Allowed Medications

3.2.1.1. Palliative and Supportive Care

Palliative and supportive care is permitted during the course of the trial for underlying conditions.

The following medications are allowed under certain circumstances and restrictions.

3.2.1.2. Cholinesterase Inhibitors

- For subjects who enter the trial receiving a cholinesterase inhibitor for at least two weeks prior to screening, the dose and schedule of their cholinesterase inhibitor is maintained stable throughout the entire Study Period, unless there is compelling medical need. Increases in cholinesterase therapy that are required as a result of inter-current illness or other medical cause of deterioration are permitted but dosing should be returned to dosing levels at trial entry as soon as feasible and the trial sponsor should be notified of the change.
- Cholinesterase inhibitor treatment must be withheld for at least 10 hours prior to QMG and MGC tests.
- If a decrease in cholinesterase inhibitor is considered based on clinical evaluation, sponsor approval must be obtained prior to the change in dose in order for the subject to remain on study. Dose increase as a result of inter-current illness or other medical cause is permitted, but dose should be returned to dose level at trial entry as soon as feasible and the trial sponsor should be notified.

3.2.1.3. Immunosuppressive Agents

The following immunosuppressive agents are allowed during the trial: corticosteroid,

AZA, MMF, MTX, tacrolimus, cyclosporine, or cyclophosphamide. The immunosuppressive agent(s) and its appropriate dose level to be used for an individual subject is at the discretion of the treating physician.

- Corticosteroid – for subjects who enter the trial receiving oral corticosteroid, *e.g.*, prednisone, the dose/schedule must have been stable for four weeks prior to trial and may not be changed during the entire double-blind Study Period. If a decrease or taper in steroid dose is considered during the Study Period based on clinical evaluation, sponsor approval must be obtained prior to the change in order for the subject to remain on trial. If the dose level subsequently must be increased, the dose level increase cannot be above the dose level reported at the baseline (at the start of randomized treatment).
- High-dose steroid should be reserved for subjects that experience Clinical Deterioration as defined by this protocol. Every effort should be made to notify the Sponsor within 24 hours of administration should a subject require a rescue therapy for Clinical Deterioration.
- AZA, MMF, MTX, tacrolimus, cyclosporine or cyclophosphamide – for subjects who enter the trial receiving above mentioned immunosuppressive agents, the dose regimen of the immunosuppressive agent may not be changed during the entire double-blind Study Period. If a change in the dose regimen is considered due to known toxicity or side effects associated with the given immunosuppressive agent, sponsor approval must be obtained prior to the dose change in order for the subject to remain on the trial. A different immunosuppressive agent cannot be added or substituted during the 26-week double-blind Study Period.

3.2.1.4. Plasma Exchange / Plasmapheresis (PE) / IVIg

Use of PE or IVIg will be allowed for subjects who experience a Clinical Deterioration as defined by this protocol. The rescue therapy used for a particular subject is at the discretion of the treating physician. Every effort should be made to notify the Sponsor within 24 hours should a subject require a rescue therapy.

If PE is administered as a rescue therapy, supplemental IP (2 vials) are administered within 60 minutes after the end of each PE session. Routine (per protocol schedule) IP administration is continued per the specified dose-administration schedule for the subject. If the subject is scheduled to receive the protocol-scheduled dose on the day of a PE session, then the scheduled dose is administered within 60 minutes after the end of the PE session.

3.2.2. Disallowed Medications

The following concurrent medications are prohibited during the trial:

- Use of

rituximab

3.3. Treatment Compliance

The infusion of IP into subjects is under the supervision of the PI/Sub-Investigator or their designee, to ensure that the subject receives the appropriate dose at the appropriate time-points during the trial.

Subjects who fail to return for a scheduled visit within the accepted intervals must be contacted by the site study staffs to determine the reason for missing the appointment. Instructions for handling of missing visits are provided in Section 1.4.2.

3.4. Randomization and Blinding

3.4.1. Randomization

Subjects are randomized on Day 1 after the Investigator has verified that they are eligible. Subjects are randomized in a 1:1 ratio of eculizumab infusion to placebo infusion. The randomization will be across centers using an IXRS. The randomization stratification will be based on MGFA clinical classification assessed at the Screening Visit according to the following 4 groupings:

a. MGFA Class IIa and IIIa
b. MGFA Class IVa
c. MGFA Class IIb and IIIb, and
d. MGFA Class IVb

The MGFA clinical classifications are described in Table 7.

3.4.2. Blinding and Unblinding

All trial subjects, investigational site personnel, sponsor staff, sponsor designees, and all staff directly associated with the conduct of the trial are blinded to the subject treatment assignments. The double blind is maintained by using identical IP kits and labels for eculizumab and placebo. The placebo has an identical appearance to that of eculizumab. The random code is maintained by Almac Clinical Services. There is no antidote to reverse the effects of eculizumab.

Therefore, unblinding would not be helpful in the planning of patient treatment for a given event. Unblinding should only be considered for the safety of the subject. If unblinding is deemed necessary by the Investigator, the Investigator can unblind the patient's treatment

allocation using IXRS. The Investigator must note the date, time and reason for unblinding.

The Investigator should inform the Medical Monitor that the patient was unblinded, however they are not required to reveal to the Medical Monitor the patients' treatment allocation.

When an AE is an unexpected related serious AE, the blind will be broken by the Sponsor only for that specific subject. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, investigators, etc.) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel. Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, Ethics Committees and/or IRBs.

Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

4. Investigational Product Materials and Management

4.1. Investigational Product

Each vial of IP contains eculizumab 300 mg or matching placebo for IV administration.

4.2. Investigational Product Packaging and Labeling

The active IP, eculizumab is manufactured and supplied by Alexion in single 30 mL vials as a solution concentration of 10 mg/ml. The comparator product is manufactured by Alexion Pharmaceuticals, Inc., as a matching sterile, clear, colorless solution with the same buffer components but without active ingredient, in an identical 30 ml vial. *See* Table 12.

All study medication is prepared in vials, packaged in kits, labeled in an identical manner.

IP vials will be individually packaged into a kit. Both vials and kits will be labeled according to the protocol and local regulatory requirements. Each kit will have a label describing the contents and a place for the pharmacist to record the subject number and initials.

Study medication is shipped and released to each participating trial center upon receipt of all required essential documents based upon federal, state, and local regulations (Table 12).

TABLE 12: INVESTIGATIONAL PRODUCT

	Investigational	
Product Name:	Eculizumab	Placebo
Dosage Form:	Concentrate for solution for infusion	Solution for infusion
Unit Dose:	300 mg	0 mg
Route of Administration:	Intravenous Infusion	Intravenous Infusion
Physical Description:	30 mL vial	30 mL vial
Manufacturer:	Alexion Pharmaceuticals, Inc.	Alexion Pharmaceuticals, Inc.

4.3. Investigational Product Storage

IP is released to the site upon receipt of all required essential documents based upon federal, state, and local regulations. *See* Table 12.

Upon arrival at the center, the IP is promptly removed from the shipping cooler and stored in refrigerated conditions at 2 to 8°C. The pharmacist should immediately record the reception of the IP and notify the distributor if vials are damaged and/or if temperature excursions have occurred during transportation. IP must be stored in a secure, limited-access storage area and temperature must be monitored daily.

Diluted solutions of IP may be stored at 2 to 8°C (36-46°F) for up to 24 hours prior to administration. If the IP is prepared more than 4 hours in advance of a subject's visit, the diluted material should be stored at 2 to 8°C. The solution should be allowed to warm to room temperature prior to administration. The material must not be heated (*e.g.*, by using a microwave or other heat source) other than by ambient air temperature.

4.4. Investigational Product Preparation

Infusions of IP are prepared using aseptic technique. Each vial of IP contains 300 mg of active ingredient in 30 mL of product solution or matching placebo.

Withdraw the required amount of IP from the vials. Transfer the recommended dose to an infusion bag. Dilute the IP to a final concentration of 5 mg/mL by addition to the infusion bag of the appropriate amount (equal volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP. The final volume of a 5 mg/mL diluted IP solution is 120 mL for 600 mg doses (2 vials), 180 mL for 900 mg doses (3 vials) and 240 mL for 1200 mg doses (4 vials) as shown in Table 13.

TABLE 13: INVESTIGATIONAL PRODUCT RECONSTITUTION

Investigational Product	Volume of IP	Volume of Diluent [a]	Total Volume of Administration
600 mg (2 vials)	60 mL	60 mL	120
900 mg (3 vials)	90 mL	90 mL	180
1200 mg (4 vials)	120 mL	120 mL	240

[a] Choose one of the following diluents: a. 0.9% sodium chloride; b. 0.45% sodium chloride; c. 5% dextrose in water; d. Ringer's injection

Gently invert the infusion bag containing the diluted IP solution to ensure thorough mixing of the product and diluents. Discard any unused portion left in a vial, as the product contains no preservatives. The diluted solution should be allowed to warm to room temperature by exposure to ambient air prior to administration.

4.5. Administration

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION

IP is only administered via IV infusion and must be diluted to a final concentration of 5 mg/mL prior to administration. Prior to administration, if the diluted solution is refrigerated, it is allowed to warm to room temperature by exposure to ambient air. The diluted solution must not be heated in a microwave or with any heat source other than ambient air temperature. Parenteral drug products are inspected visually for particulate matter and discoloration prior to administration.

The diluted IP is intravenously administered over 35 minutes (range 25 to 45 minutes). It is not necessary to protect the infusion bags from light while IP is being administered to the subject. At the site's discretion, the diluted IP may be administered via gravity feed, a syringe-type pump, or an infusion pump. The subjects are monitored for 1 hour following infusion.

If an AE occurs during the administration of the IP, the infusion may be slowed or stopped at the discretion of the Investigator, depending upon the nature and severity of the event. The overall time of infusion should not exceed 2 hours. The AE must be captured in the subject's source document and CRF.

5. Assessment of Efficacy

Duration of treatment commences with the first infusion of IP (eculizumab or placebo). The 26-week Study Period defines the time period for assessment of the study endpoints (specified in Table 6, the schedule of assessments). Efficacy will be assessed comparing eculizumab outcomes to placebo outcomes. Statistical analyses of the efficacy endpoints are summarized below and described in more detail in the statistical analysis plan. For all scales

noted below except the EQ Visual Analog Scale (VAS) and Myasthenia Gravis Foundation of America (MGFA) Post-Intervention Status (PIS) the higher the score the greater the impairment.

5.1. MG Activities of Daily Living Profile (MG-ADL)

The MG-ADL is an 8-point questionnaire that focuses on relevant symptoms and functional performance of activities of daily living (ADL) in MG subjects (*see* Table 1). The 8 items of the MG-ADL were derived from symptom-based components of the original 13-item QMG to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb (2 items) impairment related to effects from MG. In this functional status instrument, each response is graded 0 (normal) to 3 (most severe). The range of total MG-ADL score is 0 – 24. A clinically meaningful improvement in a patient's MG-ADL would be a 3 point or greater reduction in score after 26 weeks of treatment. The recall period for MG-ADL is the preceding 7 days. MG-ADL will be performed at Screening, Day 1, Weeks1-4, 8, 10, 12, 16, 20, and 26 or ET (Visits 2-6, 8, 10, 12, 14, and 17, or ET) by a properly trained evaluator, preferably the same evaluator throughout the study.

5.2. QMG Scoring System

The current QMG scoring system consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item) and respiratory (1 item); each graded 0 to 3, with 3 being the most severe (*see* Table 2). The range of total QMG score is 0 – 39. The QMG scoring system is considered to be an objective evaluation of therapy for MG and is based on quantitative testing of sentinel muscle groups. The MGFA task force has recommended that the QMG score be used in prospective studies of therapy for MG(15). A clinically meaningful improvement in a patient's QMG would be a 4 point or greater reduction in score after 26 weeks of treatment. The QMG will be administered at Screening, Day 1, Weeks 1-4, 8, 12, 16, 20, and 26 or ET (Visits 1-6, 8, 10, 12, 14, and 17 or ET).

5.3. MGC Score

The MGC is a validated assessment tool for measuring clinical status of subjects with MG (16). The MGC assesses 10 important functional areas most frequently affected by MG and the scales are weighted for clinical significance that incorporate subject-reported outcomes (*see* Table 3). A clinically meaningful improvement in a patient's MGC would be a 3 point or greater reduction in score after 26 weeks of treatment. MGC will be administered at Screening, Day 1, Weeks 1-4, 8, 12, 16, 20, and 26 or ET (Visits 1-6, 8, 10, 12, 14, and 17 or ET).

5.4. Quality of Life Assessments

5.4.1. MG-QOL 15

The 15-item Myasthenia Gravis Qualify of Life scale (MG-QOL 15) (*see* Figure 1) is a health-related quality of life evaluative instrument specific to subjects with MG. MG-QOL15 was designed to provide information about subjects' perception of impairment and disability and the degree to which disease manifestations are tolerated and to be easy to administer and interpret (17). The MG-QOL 15 is completed by the subject. Higher scores indicate greater extent of and dissatisfaction with MG-related dysfunction. A clinically meaningful improvement in a patient's MG-QOL 15 would be an increase in score after 26 weeks of treatment. The MG-QOL 15 is administered at Screening, Day 1, Weeks 4, 8, 12, 16, 20, and 26 or ET (Visits 1-2, 6, 8, 10, 12, 14, and 17 or ET).

5.4.2. Neuro-QOL Fatigue

The Neuro-QOL Fatigue is a reliable and validated brief 19-item survey of fatigue, completed by the subject (18). Higher scores indicate greater fatigue and greater impact of MG on activities (*see* Table 5). A clinically meaningful improvement in a patient's Neuro-QQL Fatigue score would be reflected in a decrease in score after 26 weeks of treatment. The Neuro-QOL Fatigue is administered at Day 1, Weeks 4, 8, 12, 16, 20, and 26 or ET (Visits 2, 6, 8, 10, 12, 14, and 17 or ET).

5.4.3. EUROQOL (EQ-5D)

The EUROQOL (EQ-5D) is a reliable and validated survey of health status in 5 areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, completed by the subject (19). Each area has 3 levels: level 1 (no problems), level 2 (some problems), and level 3 (extreme problems) (*see* Figures 2A and 2B). The EQ VAS records the subject's self-rated health on a vertical, 20 cm visual analogue scale where the endpoints are labeled "Best imaginable health state, marked as 100" and "Worst imaginable health state, marked as 0." A clinically meaningful improvement in a patient's EQ-5D would be reflected as an increase in score after 26 weeks of treatment. The EQ-5D is administered at Day 1, Weeks 4, 8, 12, 16, 20, and 26 or ET (Visits 2, 6, 8, 10, 12, 14, and 17 or ET).

5.5. Other Efficacy Assessments

5.5.1. Negative Inspiratory Force NIF and Forced Vital Capacity

Subjects with increasingly severe MG can suffer from potentially fatal respiratory complications including profound respiratory muscle weakness. Respiratory function is

monitored closely for evidence of respiratory failure in MG subjects and ventilator support is recommended in the event of consistent declines in serial measurements of Forced Vital Capacity (FVC) or Negative Inspiratory Force (NIF), loss of upper airway integrity (difficulty handling oral secretions, swallowing, or speaking) or in the setting of emerging respiratory failure. FVC as one of the test items in QMG is performed when QMG is performed. NIF was to be performed using the NIF Meter. It is measured at Screening, Day 1, Weeks 1-4, 8, 12, 16, 20, and 26 or ET (Visits 1-6, 8, 10, 12, 14, and 17 or ET).

5.5.2. MGFA Post-Intervention Status

The MG clinical state is assessed using the MGFA Post-Intervention Status. *See* Table 10. Change in status categories of Improved, Unchanged, Worse, Exacerbation and Died of MG as well as the Minimal manifestation (MM) is assessed and recorded at Weeks 4, 12 and 26 or ET (Visits 6, 10 and 17 or ET) by the PI or the same neurologist skilled in the evaluation of MG subjects throughout the trial. The sub-scores of MM, *i.e.*, MM-0, MM-1, and MM-3, will not be used in this protocol.

6.2. Determination of Sample Size

The study design is a randomized, double blind, placebo-controlled design. Subjects will be randomly assigned 1:1 to eculizumab or placebo. The randomization stratification variable will be based on MG clinical classification by the Myasthenia Gravis Foundation of America (MGFA) according to the following 4 groupings (Class IIa and IIIa, Class IVa, Class IIb and IIIb and Class IVb).

The sample size and power calculation assumptions are as follows:

- 1:1 randomization (eculizumab: placebo)
- Power 90% for both the primary and the first secondary endpoints
- Two-sided 5% level of significance
- Drop-out rate 15%
- Mean changes from baseline for MG-ADL are assumed to be 4 for eculizumab and 1.5 for placebo with a standard deviation of 3.25, mean changes in QMG total score of 7 for eculizumab and 3 for placebo with a standard deviation of 6, and mean ranked differences between the treatment groups is assumed to be 3 with a standard deviation of 4 for both endpoints. Sample size calculations based on t-test.

With these assumptions, a sample size of approximately 92 subjects (46 eculizumab and 46 placebos) provides 90% power to detect a treatment difference at 26

weeks.

6.3. Analyses Sets

Analyses are produced for the double-blind Study Period in order to compare the eculizumab group with placebo group. The analyses include efficacy, safety, and PK/PD analyses.

6.3.1. Full Analysis Set

The full analysis set (FAS) is the population on which primary, secondary, and tertiary efficacy analyses is performed and consists of all subjects who are randomized to IP and who have received at least 1 dose of IP (eculizumab or placebo treatment) and have at least one efficacy assessment post IP infusion. Subjects are compared for efficacy according to the treatment they were randomized to receive, irrespective of the treatment they actually received.

6.3.2. Per-Protocol Set

The Per-Protocol (PP) Set is a subset of the Full Analysis Set (FAS) population, excluding subjects with major protocol deviations. The possible categories of major protocol deviations are defined in the statistical analysis plan. The per-protocol population will include all subjects who:

- Have no major protocol deviations or inclusion/exclusion criteria deviations that might potentially affect efficacy,
- Subjects who took at least 80% of the required doses and remained enrolled in the trial for 26 weeks or subjects who took at least 80% of the required doses up to the time of being discontinued for Clinical Deterioration (*e.g.*, MG crisis/exacerbation).

The PP population will be fully described in the statistical analysis plan, and subjects identified prior to database lock. Efficacy analyses will also be performed on the PP data set.

6.7. Efficacy Analyses

Note: During the Study Period, Baseline is defined as the last available assessment prior to treatment for all subjects, regardless of treatment group.

6.7.1. Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline in the MG-ADL total score at Week 26 of the Study Period. The primary efficacy analysis is conducted on the available 26 week data from the Study Period for all subjects. The trial is considered to have met its

primary efficacy objective if a statistically significant difference ($p \leq 0.05$) between the eculizumab treatment group and placebo group is observed for change from baseline in the MG-ADL total score at Week 26. Confidence intervals and p-values will be presented. For the primary analysis concerning the change from baseline in the MG-ADL total score at Week 26, treatment groups are compared using a worst-rank score analysis (*i.e.*, analysis of covariance [ANCOVA] analysis with ranks) with effects for treatment. The baseline MG-ADL total score and the randomization stratification variables are also to be covariates in the model. In this analysis, the actual changes from baseline are ranked from highest (best improvement in MG-ADL score) to lowest (least improvement / most worsening in MG-ADL score) across all subjects who did not need rescue therapy. Then, any subject who needed rescue therapy would be given lower ranks. These lower ranks are based on the time to rescue therapy from the start of investigational product (Day 1). The subject with the shortest time to rescue therapy would get the absolute lowest rank in the analysis and the subject with the longest time to rescue therapy would get a rank that is one lower than the lowest ranked subject without rescue therapy. Last observation carried-forward is used for missing changes from baseline at Week 26 for patients with missing Week 26 who did not require rescue therapy.

A sensitivity analysis for the actual change from baseline in the MG-ADL total score at Week 26 is also performed. Treatment groups are compared using ANCOVA analysis using the actual change from baseline in the MG-ADL total score at Week 26 with effects for treatment. The baseline MG-ADL total score and the randomization stratification variable are also covariates in the model. Last observation carried-forward is used for missing changes from baseline at Week 26.

A sensitivity analysis for the actual change from baseline in the MG-ADL total score at Week 26 is also performed. In the sensitivity analysis, treatment groups are compared using repeated measures model with effects for treatment and visits. The baseline MG-ADL total score, the randomization stratification variable, and an indicator for the IST treatment status of the subject are also covariates in the model. Subjects have an IST treatment status variable defined based on the IST treatments the subject receives.

In addition, summaries of changes from baseline in the MG-ADL total score at Week 26 are produced by treatment group for subjects who have failed ISTs.

- Subjects who have failed treatment over one year or more with 2 or more ISTs in sequence or in combination.
- Subjects who have failed at least one IST and require chronic plasma exchange or IVIg

to control symptoms.

6.7.2. Secondary Efficacy Analysis

Unless otherwise specified, the secondary efficacy analyses use the available 26-week data from the Study Period. Hypothesis testing comparing eculizumab treatment with placebo treatment for the secondary efficacy analyses are performed using a closed testing procedure with the following rank order:

1. Change from baseline in QMG total score at Week 26
2. Proportion of subjects with at least a 3-point reduction in the MG-ADL total score from baseline to Week 26 and with no rescue therapy
3. Proportion of subjects with at least a 5-point reduction in the QMG total score from baseline to Week 26 and with no rescue therapy
4. Change from baseline in the MGC score at Week 26
5. Change from baseline in MG-QOL15 at Week 26

The hypothesis testing will proceed from highest rank (#1) Change from baseline in QMG total score at Week 26 to (#5) Change from baseline in MG-QOL-15, and if statistical significance is not achieved at an endpoint ($p \leq 0.05$), then endpoints of lower rank are not considered to be statistically significant. Confidence intervals and p-values are presented for all secondary efficacy endpoints for descriptive purposes, regardless of the outcome of the closed testing procedure.

The secondary endpoints that involve changes from baseline are analyzed using a worst-case ranked analysis of covariance (ANCOVA) like that described for the primary efficacy endpoints as the primary analysis for the particular secondary endpoint. The ranked ANCOVA will have effects for treatment, the baseline for the particular endpoint, and the randomization stratification variable.

A sensitivity analysis for the change from baseline in QMG at Week 26 is analyzed using repeated measures model with effects for treatment, visits, and baseline QMG score in order to compare treatment groups. The randomization stratification variable is also a covariate in the model. A sensitivity analysis for the actual change from baseline in QMG score at Week 26 will also be performed. Treatment groups are compared using ANCOVA analysis using the actual change from baseline in the QMG score at Week 26 with effects for treatment. The baseline QMG score and the randomization stratification variable are also covariates in the model. Last observation carried-forward will be used for missing changes from baseline at Week 26.

A sensitivity analysis for the change from baseline in MGC at Week 26 is analyzed using repeated measures model with effects for treatment, visits, and baseline MGC score in order to compare treatment groups. The randomization stratification variable is also a covariate in the model.

A sensitivity analysis for the change from baseline in MG-QOL-15 at Week 26 is analyzed using repeated measures model with effects for treatment, visits, and baseline MG-QOL-15 score in order to compare treatment groups. The randomization stratification variable is also a covariate in the model.

The proportion of subjects with at least a 3 point reduction in the MG-ADL total score from baseline to Week 26 with no rescue therapy are analyzed by the Cochran-Mantel-Haenszel test stratified by randomization stratification variable in order to compare eculizumab versus placebo.

The proportion of subjects with at least a 5 point reduction in the QMG total score from baseline to Week 26 with no rescue therapy are analyzed by the Cochran-Mantel-Haenszel test stratified by randomization stratification variable in order to compare eculizumab versus placebo.

Additional sensitivity analyses are performed in order that assess the impact of IST treatment status on the various secondary endpoints. A sensitivity analysis for the change from baseline in the secondary endpoints (*i.e.*, QMG, MGC, and MG-QOL-15) at Week 26 are analyzed using repeated measures model with effects for treatment, visits, and baseline score in order to compare treatment groups. The randomization stratification variable and an indicator for the IST treatment status of the subject are also covariates in the model. Subjects will have an IST treatment status variable defined based on the IST treatments the subject receives.

In addition, summaries of changes from baseline in QMG, MGC, and MG-QOL-15 at Week 26 are produced by treatment group for subjects who have failed ISTs.

- Subjects who have failed treatment over one year or more with 2 or more ISTs in sequence or in combination
- Subjects who have failed at least one IST and require chronic plasma exchange or IVIg to control symptoms.

6.7.3. Tertiary Efficacy Endpoints

The tertiary efficacy analyses for the Study Period include the following:

1. Time to response as measured by the reduction in the MG-ADL total score (3-

point reduction from baseline)

2. Change from baseline in Neuro-QOL Fatigue at Week 26
3. Change from baseline in EQ-5D at 26 weeks
4. Change from baseline in NIF at Week 26 in subjects with abnormal NIF at baseline
5. Change from baseline in FVC at Week 26 in subjects with abnormal FVC at baseline
6. Change from baseline in the MG-ADL individual items and change from baseline in the MG-ADL sub-categories for the bulbar (items 1, 2 and 3), respiratory (item 4), limb (items 5 and 6) and ocular (items 7 and 8) at Week 26 in subjects with an abnormal baseline score for the particular item or sub-category
7. Change from baseline in the MGFA Post-Intervention Status at Week 26.

For the time to response on the MG-ADL total score (3-point reduction in MG-ADL from baseline), treatment groups are compared using Cox PH regression with robust variance estimation. The randomization stratification variable is also a covariate in the model. Inference is based on the Wald test of the log hazard ratio.

Quality of life is summarized as appropriate to the quality of life instrument and treatment group comparisons is performed as specified in the statistical analysis plan (SAP).

The tertiary endpoints that involve changes from baseline are analyzed using a worst-case ranked ANCOVA like that described for the primary efficacy endpoints as the primary analysis for the particular tertiary endpoint. The ranked ANCOVA has effects for treatment, the baseline for the particular endpoint, and the randomization stratification variable.

A sensitivity analysis for the change from baseline in NIF at Week 26 for subjects with abnormal NIF at baseline is analyzed using repeated measures model with effects for treatment, visits, and baseline NIF in order to compare treatment groups. The randomization stratification variables are also covariates in the model.

A sensitivity analysis for the change from baseline in FVC is analyzed using repeated measures model with effects for treatment, visits, and baseline FVC in order to compare treatment groups. The randomization stratification variable is also a covariate in the model.

A sensitivity analysis for the change from baseline in the MG-ADL individual items and sub-categories at Week 26 in subjects that are abnormal at baseline are analyzed using repeated measures model with effects for treatment, visits, and baseline

MG-ADL individual item and sub-categories, as applicable for the analysis, in order to compare treatment groups. The randomization stratification variable is also a covariate in the model. In addition, for all full analysis set (FAS) and all PP subjects, a sensitivity analysis for the change from baseline in the MG-ADL individual items and sub-categories at Week 26 are performed using repeated measures model with effects for treatment, visits, and baseline MG-ADL individual item or sub-categories score, as applicable for the analysis, in order to compare treatment groups. The randomization stratification variable is also a covariate in the model. Finally, similar sensitivity analyses and/or summaries are produced (depending on the number of subjects) in the subset of subjects who were normal at baseline and became abnormal after baseline in the MG-ADL individual items and sub-categories.

A summary of subjects going from normal to abnormal for NIF and FVC are presented. A summary of subjects going from normal to abnormal for a particular MG-ADL individual items and sub-categories are produced.

6.11. Other Statistical Issues

6.11.1. Significance Levels

For all analyses, the eculizumab treated group is compared to the placebo group and all hypothesis testing is two-sided and performed at the 0.05 level of significance, unless otherwise specified. Estimates of treatment effect on efficacy parameters are accompanied by two-sided 95% confidence intervals for the effect size.

6.11.2. Missing or Invalid Data

For efficacy and safety analyses, missing post-baseline efficacy and safety data are not imputed unless indicated in the described analysis in the SAP.

6.11.3. Interim Analysis

There is no interim analysis planned for this trial.

Example 2: Extension Trial

An extension trial is described herein that was run to evaluate the long-term safety of eculizumab in subjects with refractory gMG. Other secondary objectives include:

- Evaluation of the long-term efficacy as measured by MG-ADL
- Evaluation of long-term efficacy by additional efficacy measures including:

- QMG, MGC,
- MG-ADL individual items and subcategories
- Quality of life

- Description of the PK and PD of eculizumab in refractory gMG patients.

The extension trial lasts for 4 years (FPFV to LPLV). The first visit occurs within 2 weeks of Visit 17 (Week 26) in the trial described above. To maintain the blind of the previous trial, all subjects undergo a blind induction phase, followed by an open label maintenance phase. This is summarized in Figures 6 and 7. "Home infusion" at selected visits is performed with permission of the primary investigator in accordance with regulations. Assessments, Treatment, Concomitant/Prohibited medications were performed as in the study described above.

The inclusion criteria for the extension trial was completion of the previous trial. Exclusion criteria were withdrawing from the previous trial and pregnancy or intention to get pregnant. IST treatment could be changed at the treating physician's discretion but rituximab was prohibited.

Efficacy was measured by MG-ADL, QMG, MGC, NIF, FVC, QOL, G-QOL15, Neuro-QOL Fatigue, EQ-5D and MGFA Post-Intervention Status.

Example 3: Results from REGAIN Study Comprising ECU-MG-301 26 Week (301) Trial and ECU-MG-302 Extension (302) Trial

The REGAIN study is a randomized, double-blind, placebo-controlled, multicenter trial evaluating the safety and efficacy of eculizumab in patients with refractory gMG. The study enrolled and treated 125 adult patients across North America, South America, Europe, and Asia. Patients had a confirmed MG diagnosis with positive serologic test for anti-AChR antibodies. All patients had previously failed treatment with at least two immunosuppressive agents or failed treatment with at least one immunosuppressive agent and required chronic plasma exchange or IVIg, and had an MG-ADL total score $\geq$6 at study entry.

As discussed above the patients were initially randomized according to MGFA Clinical Classification shown in Table 7 into the following four groups:

MGFA IIa/IIIa

MGFA IIb/IIIB

MGFA IVa

MGFA IVb

The breakdown of the MGFA classification at screening was as follows: Class IIa 25 total patients; Class IIb 22 total patients; Class IIIa 36 total patients; Class IIIb 30 total patients; Class IVa 6 total patients; and Class IVb 6 total patients.

The patients were assigned to the placebo group as follows: Class IIa 15 (23.8%) total patients; Class IIb 14 (22.2%) total patients; Class IIIa 16 (25.4%) total patients; Class IIIb 13 (20.6%) total patients; Class IVa 2 (3.2%) total patients; and Class IVb 3 (4.8%) total patients.

The patients were assigned to the eculizumab group were as follows: Class IIa 10 (16.1%) total patients; Class IIb 8 (12.9%) total patients; Class IIIa 20 (32.3%) total patients; Class IIIb 17 (27.4%) total patients; Class IVa 4 (6.5%) total patients; and Class IVb 3 (4.8%) total patients.

The disposition of patients completing the 301 trial and entering the 302 trial is shown below in Table 14.

TABLE 14: PATIENT DISPOSITION IN THE 301 AND 302 TRIALS

Status	Placebo n (%)	Eculizumab n (%)	Total n (%)
Randomized	63 (100.0)	63 (100.0)	126 (100.0)
Treated	63 (100.0)	62 (98.4)	125 (99.2)
Completed the Study	61 (96.8)	57 (90.5)	118 (93.7)
Discontinued	2 (3.2)	6 (9.5)	8 (6.3)
Adverse Event	0 (0.0)	4 (6.3)	4 (3.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by Subject	2 (3.2)	1 (1.6)	3 (2.4)
Other	0 (0.0)	1 (1.6)	1 (0.8)
Enrolled in Open-Label Extension Study	61 (96.8)	56 (88.9)	117 (92.9)

Therefore 96.8 % of the placebo patients and 88.9% of the eculizumab patients proceeded into the extension trial.

The demographics of the 301 trial participants were as is shown below in Table 15.

TABLE 15: DEMOGRAPHICS OF 301 CLINICAL TRIAL PARTICIPANTS

Variable	Statistic	Placebo (N=63)	Eculizumab (N=62)	Total (N=125)
Age at First IP Dose (years) (1)	n	63	62	125
	Mean (SD)	46.9 (17.98)	47.5 (15.66)	47.2 (16.80)
	Median	48.0	44.5	46.0
	Min, Max	19, 79	19, 74	19, 79
Sex				
Male	n (%)	22 (34.9)	21 (33.9)	43 (34.4)
Female	n (%)	41 (65.1)	41 (66.1)	82 (65.6)
Race				
Asian	n (%)	16 (25.4)	3 (4.8)	19 (15.2)
Black or African American	n (%)	3 (4.8)	0 (0.0)	3 (2.4)
White	n (%)	42 (66.7)	53 (85.5)	95 (76.0)
Other	n (%)	2 (3.2)	6 (9.7)	8 (6.4)
Is the subject of Japanese descent?				
Yes	n (%)	9 (14.3)	3 (4.8)	12 (9.6)
No	n (%)	54 (85.7)	59 (95.2)	113 (90.4)

The protocol defines clinical deterioration as a subject who has one of the following:

1. MG Crisis

2. Significant symptomatic worsening, defined as worsening on any one of the MG-ADL individual items excluding ocular (*i.e.*, talking, chewing, swallowing, breathing, upper and lower extremity weakness):

- To Grade 3, or

-2-point worsening in MG-ADL

3. The treating physician believes that the subject's health is in jeopardy if rescue therapy is not administered.

Rescue therapy is defined in the protocol as follows: Use of PE or IVIg will be allowed for subjects who experience a Clinical Deterioration as defined by this protocol. The rescue therapy used for a particular subject is at the discretion of the treating physician

If PE is administered as a rescue therapy, supplemental IP (2 vials) are administered

within 60 minutes after the end of each PE session. Routine (per protocol schedule) IP administration is continued per the specified dose-administration schedule for the subject. If the subject is scheduled to receive the protocol-scheduled dose on the day of a PE session, then the scheduled dose is administered within 60 minutes after the end of the PE session.

The total numbers of patients who experienced clinical deterioration during the protocol were as is shown below in Table 16.

TABLE 16: CLINICAL DETERIORATION DURING THE 301

Variable	Statistic	Placebo (N=63)	Eculizumab (N=62)
Total Number of Subjects Reporting Clinical Deterioration	n (%)	15 (23.8)	6 (9.7)
Total Number of Subjects Experiencing Clinical Deterioration Per Protocol Criteria	n (%)	11 (17.5)	6 (9.7)
Total Number of Subjects Experiencing the Following Events:			
MG Crisis	n (%)	0 (0.0)	1 (1.6)
Significant symptomatic worsening	n (%)	9 (14.3)	4 (6.5)
Subject's health is in jeopardy	n (%)	3 (4.8)	2 (3.2)
Other	n (%)	4 (6.3)	0 (0.0)
Total Number of Clinical Deterioration Events:	n	27	13
MG Crisis	n	0	1
Significant symptomatic worsening	n	14	4
Subject's health is in jeopardy	n	7	8
Other	n	6	0

The clinical deteriorations requiring rescue therapy are shown in Table 17 below:

TABLE 17: CLINICAL DETERIORATION REQUIRING RESCUE THERAPIES DURING THE 301

Variable	Statistic	Placebo (N=63)	Eculizumab (N=62)
Total Number of Subjects Requiring Rescue Therapy:	n (%)	12 (19.0)	6 (9.7)
Total Number of Subjects Requiring High Dose Corticosteroids	n (%)	5 (7.9)	0 (0.0)
Total Number of Subjects Requiring Plasmapheresis/Plasma Exchange	n (%)	4 (6.3)	3 (4.8)
Total Number of Subjects Requiring IVIg	n (%)	6 (9.5)	4 (6.5)
Total Number of Subjects Requiring Other Rescue Therapy	n (%)	2 (3.2)	1 (1.6)
Total Number of Clinical Deterioration Events Requiring Rescue Therapy:	n	24	13
Total Number of Clinical Deterioration Events Requiring High Dose Corticosteriods	n	8	0
Total Number of Clinical Deterioration Events Requiring Plasmapheresis/Plasma Exchange	n	10	4
Total Number of Clinical Deterioration Events Requiring IVIg	n	13	10
Total Number of Clinical Deterioration Events Requiring Other Rescue Therapy	n	2	2

The primary and secondary endpoints as described above were used as shown below:

- Primary Endpoint:
  - Change from baseline in MG-ADL Total Score at Week 26
- Secondary Endpoints (hierarchal):
  - Change from baseline in QMG Total Score at Week 26
  - Proportion of subjects with ≥ 3-point reduction in MG-ADL Total Score from baseline to Week 26 and without rescue therapy
  - Proportion of subjects with ≥ 5-point reduction in QMG Total Score from baseline to Week 26 and without rescue therapy
  - Change from baseline in the Myasthenia Gravis Composite (MGC) Total Score at Week 26
  - Change from baseline in MG-QoL15 at Week 26

One primary endpoint in the MG-ADL score at week 26. The score ranges from 0-24 and contains 3 bulbar items, 1 respiratory item, 2 gross motor or limb items, and 2 ocular items. A clinically meaningful improvement in MG-ADL is defined as a 3 points or greater reduction. *See* Table 1.

TABLE 18: MG-ADL WORST RANK ANALYSIS: SAP3 PER PROTOCOL SET

Variable	Statistic	Placebo (N=56)	Eculizumab (N=54)	Difference in LS Means and 95% CI	p-value
Worst Ranked Change from Baseline	Ranked Score LS Mean (SEM)	61.3 (4.10)	48.4 (4.20)	-12.8	0.0305
	95% CI for LS Mean	(53.15, 69.39)	(40.11, 56.74)	(-24.46, -1.24)	
Baseline MG-ADL Total Score for patients not needing rescue therapy or dropping out of the study	n	48	49		
	Mean (SD)	9.8 (2.70)	10.1 (3.07)		
	Median	9.0	10.0		
	Min, Max	5, 18	5, 18		
Week 26 MG-ADL Total Score (LOCF) for patients not needing rescue therapy or dropping out of the study	n	48	49		
	Mean (SD)	7.0 (3.37)	5.5 (4.04)		
	Median	6.0	5.0		
	Min, Max	2, 16	0, 15		
Change from Baseline to Week 26 in MG-ADL Total Score for patients not needing rescue therapy or dropping out of the study	n	48	49		
	Mean (SD)	-2.8 (3.05)	-4.7 (4.35)		
	Median	-2.0	-4.0		
	Min, Max	-8, 7	-15, 4		

The results from the patients who finished the entire protocol are shown in Table 18. Therefore, as shown in Table 20 the median value for the eculizumab group showed a -4 reduction in MG-ADL. This result demonstrates eculizumab produced a clinically meaningful improvement in MG patients as measured by their MG-ADL score.

The data were analyzed in multiple ways for statistical purposes as shown in Tables 18, 19, 20, and 21, but in each case the eculizumab group produced clinically meaningful improvement in MG-ADL and the placebo group failed to produce clinically meaningful improvement in MG-ADL. *See* Tables 18-21.

TABLE 19: MG-ADL WORST RANK ANALYSIS: SAP3 FULL ANALYSIS SET

Variable	Statistic	Placebo (N=63)	Eculizumab (N=62)	Difference in LS Means and 95% CI	p-value
Worst Ranked Change from Baseline	Ranked Score LS Mean (SEM)	68.3 (4.49)	56.6 (4.53)	-11.7	0.0698
	95% CI for LS Mean	(59.43, 77.20)	(47.66, 65.61)	(-24.33, 0.96)	
Baseline MG-ADL Total Score for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	9.9 (2.64)	10.1 (3.00)		
	Median	9.0	10.0		
	Min, Max	5, 18	5, 18		
Week 26 MG-ADL Total Score (LOCF) for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	7.0 (3.36)	5.4 (4.05)		
	Median	6.0	5.0		
	Min, Max	2, 16	0, 15		
Change from Baseline to Week 26 in MG-ADL Total Score for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	-2.8 (3.07)	-4.7 (4.32)		
	Median	-2.0	-4.5		
	Min, Max	-8, 7	-15, 4		

Refractory gMG is an ultra-rare segment of MG—a debilitating, complement-mediated neuromuscular disease—in which patients have largely exhausted conventional therapy and continue to suffer profound muscle weakness throughout the body, resulting in slurred speech, impaired swallowing and choking, double vision, upper and lower extremity weakness, disabling fatigue, shortness of breath due to respiratory muscle weakness, and episodes of respiratory failure. In the study, the primary efficacy endpoint of change from baseline in Myasthenia Gravis-Activities of Daily Living Profile (MG-ADL) total score, a patient-reported assessment, at week 26, did not reach statistical significance (p=0.0698) as measured by a worst-rank analysis.

TABLE 20: MG-ADL ANCOVA ACTUAL CHANGES FULL ANALYSIS SET

Variable	Statistic	Placebo (N=63)	Eculizumab (N=62)	Difference in LS Means and 95% CI	p-value
Change from Baseline	LS Mean (SEM)	-2.6 (0.48)	-4.0 (0.48)	-1.4	0.0390
	95% CI for LS Mean	(-3.52, -1.63)	(-4.96, -3.04)	(-2.77, -0.07)	
Baseline MG-ADL Total Score	n	63	62		
	Mean (SD)	9.9 (2.58)	10.5 (3.06)		
	Median	9.0	10.0		
	Min, Max	5, 18	5, 18		
Week 26 MG-ADL Total Score (LOCF)	n	63	62		
	Mean (SD)	7.4 (3.50)	6.4 (4.76)		
	Median	7.0	6.0		
	Min, Max	0, 16	0, 17		
Change from Baseline	n	63	62		
	Mean (SD)	-2.4 (3.32)	-4.1 (4.48)		
	Median	-2.0	-4.0		
	Min, Max	-8, 7	-15, 4		

TABLE 21: MG-ADL ANCOVA ACTUAL CHANGES PER PROTOCOL SET

Variable	Statistic	Placebo (N=56)	Eculizumab (N=54)	Difference in LS Means and 95% CI	p-value
Change from Baseline	LS Mean (SEM)	-2.6 (0.48)	-4.3 (0.49)	-1.7	0.0153
	95% CI for LS Mean	(-3.54, -1.63)	(-5.25, -3.30)	(-3.05, -0.33)	
Baseline MG-ADL Total Score	n	56	54		
	Mean (SD)	9.9 (2.63)	10.3 (3.04)		
	Median	9.0	10.0		
	Min, Max	5, 18	5, 18		
Week 26 MG-ADL Total Score (LOCF)	n	56	54		
	Mean (SD)	7.4 (3.39)	6.0 (4.36)		
	Median	7.0	6.0		
	Min, Max	2, 16	0, 17		
Change from Baseline	n	56	54		
	Mean (SD)	-2.4 (3.16)	-4.3 (4.47)		
	Median	-2.0	-4.0		
	Min, Max	-8, 7	-15, 4		

Next the QMG scores were evaluated for all study participants. The current QMG scoring system consists of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item) and respiratory (1 item); each graded 0 to 3, with 3 being the most severe (*see* Table 2). The range of total QMG score is 0 – 39. The QMG scoring system is considered to be an objective evaluation of therapy for MG and is based on quantitative testing of sentinel muscle groups. The MGFA task force has recommended that the QMG score be used in prospective studies of therapy for MG. A clinically meaningful improvement in a patient's QMG would be a 5 point or greater reduction in score after 26 weeks of treatment.

The QMG score for the full data set was -5 in the eculizumab treated group and therefore resulted in a clinically significant improvement for all patients not needing rescue or dropping out of the study. *See* Table 22 below and Figure 11 for the results.

TABLE 22: QMG WORST RANK ANALYSIS: SAP3 FULL ANALYSIS SET

Variable	Statistic	Placebo (N=63)	Eculizumab (N=62)	Difference in LS Means and 95% CI	p-value
Worst Ranked Change from Baseline	Ranked Score LS Mean (SEM)	70.7 (4.46)	54.7 (4.50)	-16.0	0.0129
	95% CI for LS Mean	(61.85, 79.51)	(45.82, 63.64)	(-28.48, -3.43)	
Baseline QMG Total Score for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	16.4 (5.76)	17.1 (4.96)		
	Median	15.0	17.0		
	Min, Max	8, 34	6, 31		
Week 26 QMG Total Score (LOCF) for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	14.1 (5.40)	11.7 (5.83)		
	Median	13.0	12.0		
	Min, Max	5, 32	1, 27		
Change from Baseline to Week 26 in QMG Total Score for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	-2.4 (3.70)	-5.4 (4.80)		
	Median	-3.0	-5.0		
	Min, Max	-11, 8	-16, 2		

Next, the MGC score was evaluated for all study participants over time. The MGC is a validated assessment tool for measuring clinical status of subjects with MG (16). The MGC assesses 10 important functional areas most frequently affected by MG and the scales are weighted for clinical significance that incorporate subject-reported outcomes (*see* Table 3). MGC will be administered at Screening, Day 1, Weeks 1-4, 8, 12, 16, 20, and 26 or ET (Visits 1-6, 8, 10, 12, 14, and 17 or ET). Total scores range from 0-50. A clinically meaningful improvement in a patient's MGC would be a 3 point or greater reduction in score after 26 weeks of treatment.

TABLE 23: MG COMPOSITE WORST RANK ANALYSIS: SAP3 FULL ANALYSIS SET

Variable	Statistic	Placebo (N=63)	Eculizumab (N=62)	Difference in LS Means and 95% CI	p-value
Worst Ranked Change from Baseline	Ranked Score LS Mean (SEM)	67.7 (4.47)	57.3 (4.52)	-10.5	0.1026
	95% CI for LS Mean	(58.89, 76.57)	(48.32, 66.21)	(-23.07, 2.13)	
Baseline MGC Total Score for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	19.0 (6.19)	19.4 (5.97)		
	Median	19.0	20.0		
	Min, Max	7, 40	7, 35		
Week 26 MGC Total Score (LOCF) for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	13.0 (6.96)	10.3 (7.00)		
	Median	12.0	9.5		
	Min, Max	3, 37	0, 28		
Change from Baseline to Week 26 in MGC Total Score for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	-6.0 (6.19)	-9.2 (8.08)		
	Median	-6.0	-10.0		
	Min, Max	-21, 13	-24, 17		

The MGC score for the full data set was (-10) in the eculizumab treated group and therefore resulted in a clinically significant improvement for all patients not needing rescue or dropping out of the study. *See* Table 23 above for the results.

The 15-item Myasthenia Gravis Qualify of Life scale (MG-QOL 15) is a health-related quality of life evaluative instrument specific to subjects with MG. *See* Table 4. MG-QOL15 was designed to provide information about subjects' perception of impairment and disability

and the degree to which disease manifestations are tolerated and to be easy to administer and interpret. The MG-QOL 15 is completed by the subject. Total scores range from 0 to 60 and higher scores indicate greater extent of and dissatisfaction with MG-related dysfunction. A clinically meaningful improvement in a patient's MGQOL would be a decrease in score after 26 weeks of treatment.

The MG-QOL15 median score for the full data set was (-11.5) in the eculizumab treated group and therefore resulted in a clinically significant improvement for all patients not needing rescue or dropping out of the study. *See* Table 24 below for the results.

TABLE 24: MG-QOL15 WORST RANK ANALYSIS FULL ANALYSIS SET

Variable	Statistic	Placebo (N=63)	Eculizumab (N=62)	Difference in LS Means and 95% CI	p-value
Worst Ranked Change from Baseline	Ranked Score LS Mean (SEM)	69.7 (4.51)	55.5 (4.55)	-14.3	0.0281
	95% CI for LS Mean	(60.79, 78.66)	(46.43, 64.47)	(-26.98, -1.56)	
Baseline MG-QOL15 Total Score for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	30.2 (13.10)	31.5 (11.82)		
	Median	30.0	32.0		
	Min, Max	6, 60	6, 59		
Week 26 MG-QOL15 Total Score (LOCF) for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	23.7 (13.38)	18.0 (14.37)		
	Median	20.0	16.0		
	Min, Max	3, 58	0, 59		
Change from Baseline to Week 26 in MG-QOL15 Total Score for patients not needing rescue therapy or dropping out of the study	n	51	52		
	Mean (SD)	-6.5 (9.40)	-13.5 (14.07)		
	Median	-6.0	-11.5		
	Min, Max	-30, 16	-44, 19		

The Neuro-QOL Fatigue is a reliable and validated brief 19-item survey of fatigue completed by the subject. Higher scores indicate greater fatigue and greater impact of MG on activities (*see* Table 5). A clinically meaningful improvement in a patient's Neuro-QQL Fatigue score would be reflected in a decrease in score after 26 weeks of treatment.

As shown in Table 25 below, the eculizumab treated group realized a clinically meaningful improvement (reduction) in their Neuro-QQL Fatigue score after 26 weeks of treatment.

TABLE 25: NEURO FATIGUE QOL WORST RANK ANALYSIS FULL ANALYSIS SET

Variable	Statistic	Placebo (N=63)	Eculizumab (N=62)	Difference in LS Means and 95% CI	p-value
Worst Ranked Change from Baseline	Ranked Score LS Mean (SEM)	74.1 (6.26)	58.5 (6.06)	-15.6	0.0145
	95% CI for LS Mean	(61.73, 86.53)	(46.49, 70.48)	(-28.13, -3.15)	
Baseline Neuro-QOL Fatigue Total Score for patients not needing rescue therapy or dropping out of the study	n	49	51		
	Mean (SD)	61.7 (15.36)	61.8 (13.57)		
	Median	65.0	62.0		
	Min, Max	29, 88	36, 92		
Week 26 Neuro-QOL Fatigue Total Score (LOCF) for patients not needing rescue therapy or dropping out of the study	n	49	51		
	Mean (SD)	52.6 (18.66)	43.6 (19.44)		
	Median	55.0	38.0		
	Min, Max	21, 85	19, 95		
Change from Baseline to Week 26 in Neuro-QOL Fatigue Total Score for patients not needing rescue therapy or dropping out of the study	n	49	51		
	Mean (SD)	-9.1 (14.58)	-18.2 (19.60)		
	Median	-8.0	-16.0		
	Min, Max	-51, 20	-59, 30		

Discussion of the Significance of the REGAIN Study

The first prospectively defined secondary efficacy endpoint of change from baseline in Quantitative Myasthenia Gravis (QMG) total score, a physician-administered assessment of MG clinical severity, with eculizumab treatment compared to placebo at week 26, achieved a p-value of 0.0129 as measured by a worst-rank analysis. In addition, the second and third prospectively defined secondary efficacy endpoints of responder status in MG-ADL and QMG achieved p-values of <0.05: the proportion of patients with at least a 3-point reduction in MG-ADL total score and no rescue therapy from baseline to week 26 with eculizumab treatment, compared to placebo, achieved a p-value of 0.0229, and the proportion of patients with at least

a 5-point reduction in QMG total score and no rescue therapy from baseline to week 26 with eculizumab treatment compared to placebo achieved a p-value of 0.0018.

It is encouraging that the REGAIN study achieved clinically meaningful improvements in MG-ADL and QMG measures in patients treated with eculizumab compared with placebo. The magnitude of effect on QMG observed in this large, prospective registration trial is unprecedented in more than 30 years of clinical investigation of refractory MG patients. There is an urgent need in the MG community for a therapy with the potential to dramatically improve the lives of patients with refractory gMG, who continue to experience profound complement-mediated muscle weakness that makes it difficult or impossible to perform simple daily activities, including walking, talking, swallowing, and even breathing normally.

Pre-specified sensitivity analyses were prospectively defined to validate results for the primary and first secondary endpoints. Three of the four prospectively defined MG-ADL sensitivity analyses achieved p-values <0.05, including the sensitivity analysis around the primary endpoint for change from baseline in MG-ADL using repeated measures, which showed a mean change with eculizumab treatment at week 26 of -4.2 versus a mean change with placebo at week 26 of -2.3 and achieved a p-value of 0.0058. Additionally, all four prospectively defined QMG sensitivity analyses achieved p-values <0.05, including the sensitivity analysis around the first secondary endpoint for change from baseline in QMG using repeated measures, which showed a mean change with eculizumab treatment at week 26 of -4.6 versus a mean change with placebo at week 26 of -1.6 and achieved a p-value of 0.0006.

The findings from this study underscore the pivotal role of complement inhibition in addressing the underlying pathophysiology of refractory gMG. Importantly, the totality of data including the first three secondary endpoints and a series of prospectively defined sensitivity analyses, shows early and sustained substantial improvements over 26 weeks for patients treated with eculizumab compared to placebo

Example 4: Anti-C5 Antibodies for Use in Treating Refractory Myasthenia Gravis

Table 27 below contains sequences of anti-complement protein C5 specific humanized antibodies that can be used in treating refractory MG. The antibody was an anti-C5 antibody such as eculizumab having three heavy chain complementarity determining regions (CDRs) as set forth in Table 27 using the Kabat definitions of CDRs as heavy chain CDR1 in SEQ ID NO: 1, heavy chain CDR2 in SEQ ID NO: 2, and heavy chain CDR3 in SEQ ID NO: 3. The

eculizumab light chain CDRs are set forth below as as light chain CDR1 in SEQ ID NO: 4, light chain CDR2 in SEQ ID NO: 5 and light chain CDR3 in SEQ ID NO: 6. The heavy chain variable region of eculizumab is set forth in SEQ ID NO: 7 and the light chain variable region of eculizumab is set forth in SEQ ID NO: 8. The complete heavy chain of eculizumab is set forth below as SEQ ID NO: 10 and the light chain is set forth below as SEQ ID NO: 11

The antibody may be an eculizumab variant known as BNJ441 and having selected mutations in the CDR regions combined with mutations in the Fc region to increase the T1/2 of the antibody in the patient. The BNJ441 antibody has heavy chain variable region as set forth in SEQ ID NO: 12 and the light chain variable region of BNJ441 is set forth in SEQ ID NO: 8. The complete heavy chain of BNJ441 is set forth below as SEQ ID NO: 14 and the light chain is set forth below as SEQ ID NO: 11

The antibody may be an anti-C5 antibody unrelated to eculizumab such as the 7086 antibody and having three heavy chain complementarity determining regions (CDRs) as set forth in Table Table 27 using the Kabat definitions of CDRs as heavy chain CDR1 in SEQ ID NO: 21, heavy chain CDR2 in SEQ ID NO: 22, and heavy chain CDR3 in SEQ ID NO: 23. The 7086 antibody light chain CDRs are set forth below as light chain CDR1 in SEQ ID NO: 24, light chain CDR2 in SEQ ID NO: 25 and light chain CDR3 in SEQ ID NO: 26. The heavy chain variable region of 7086 is set forth in SEQ ID NO: 27 and the light chain variable region of 7086 is set forth in SEQ ID NO: 28.

The antibody may be an anti-C5 antibody unrelated to eculizumab such as the 8110 antibody and having three heavy chain complementarity determining regions (CDRs) as set forth in Table 27 using the Kabat definitions of CDRs as heavy chain CDR1 in SEQ ID NO: 29, heavy chain CDR2 in SEQ ID NO: 30, and heavy chain CDR3 in SEQ ID NO: 31. The 7086 antibody light chain CDRs are set forth below as light chain CDR1 in SEQ ID NO: 32, light chain CDR2 in SEQ ID NO: 33 and light chain CDR3 in SEQ ID NO: 34. The heavy chain variable region of 8110 is set forth in SEQ ID NO: 35 and the light chain variable region of 8110 is set forth in SEQ ID NO: 36.

The antibody may be an anti-C5 antibody or antigen binding fragment thereof comprising a heavy chain variable region amino acid sequence according to SEQ ID NO: 37 and a light chain variable region amino acid sequence according to SEQ ID NO: 38.

Example 5: Dual Responder Analyses of Both Muscle Strength and Activities of Daily Living, Eculizumab Versus Placebo, in Refractory Generalized Myasthenia Gravis (gMG) Patients: Results from the REGAIN Study

The objective of the example was to assess the time course of response in patients who demonstrated a clinically meaningful response to eculizumab and the proportion of patients who had clinically meaningful relevant responses on both the MG-ADL and the QMG. Patients with refractory gMG continued to receive stable doses of ISTs (including corticosteroids) throughout the study; patients were randomized to receive blinded eculizumab 900 mg weekly for 4 weeks, 1200 mg on the fifth week, and then 1200 mg every 2 weeks thereafter (n = 62) or blinded placebo (n = 63) (Figure 12).

The Myasthenia Gravis Activities of Daily Living (MG-ADL) is a physician-directed, patient-reported measure of symptom severity related to MG-specific ADLs (Muppidi, *Ann. N.Y. Acad. Sci.* 1274: 114-19 (2012)), and the Quantitative Myasthenia Gravis (QMG) tool is a clinician-reported measure of muscle strength (Barohn *et al.*, *Ann. N.Y. Acad. Sci.* 841: 769-72 (1998)). Pre-specified responder analyses included the proportion of patients who responded with ≥3-point improvement in MG-ADL total score with no rescue; and the proportion of patients with ≥5-point improvement in QMG total score with no rescue. In an ad hoc dual responder analysis, response was defined as an improvement of ≥3 points from baseline in the MG-ADL total score and improvement of ≥5 points from baseline in the QMG total score, with no rescue therapy. In addition to the prespecified responder thresholds (*i.e.*, ≥3-point improvement for MG-ADL and ≥5-point improvement for QMG), thresholds of ≥4, 5, 6, 7, and 8 for MG-ADL and ≥6, 7, 8, 9, and 10 for QMG were also examined. *P* values from a Cochran–Mantel–Haenszel (CMH) test were provided for the more stringent criteria to aid interpretation.

More patients receiving eculizumab than those who received placebo experienced clinically meaningful responses as defined above, and also clinically meaningful relevant responses based on the more stringent thresholds for both MG-ADL and QMG total scores (Figure 13). MG-ADL responder analyses conducted at each assessment date over the 26-week study are shown in Figure 14 (the proportion of patients with a ≥3, 5, or 8 point change in the MG-ADL). QMG responder analyses conducted at each assessment date over the 26-week study are shown in Figure 15 (the proportion of patients with a greater than 5, 7, or 10 point change in the QMG). There was a substantial overlap of patients who achieved a clinically meaningful response in both the MG-ADL total score and QMG total score (Figure 16). For each of the categorical thresholds of response, a >3-fold increase was seen in the proportion of improved

patients in the eculizumab group compared with those in the placebo group (Figure 16). More patients receiving eculizumab versus placebo achieved clinically meaningful responses at week 26 in both the MG-ADL and QMG scores (week 26: eculizumab 40% vs placebo 13%; nominal $P < 0.001$) (Figure 16). The benefit of eculizumab treatment was apparent within the first 2 weeks (week 2: eculizumab 19% vs placebo 6% were dual responders; nominal $P = 0.0297$) and was sustained through week 26 (all $P \leq 0.05$) (Figure 17).

Three times as many patients with refractory gMG who were treated with eculizumab experienced clinically meaningful improvements in both muscle strength and ADLs compared with the placebo group by week 26. An increased proportion of individual assessment responders (on both the MG-ADL and the QMG) as well as dual responders occurred in the eculizumab-treated patient group compared with the placebo group which was observed early and generally maintained over the course of the study.

As shown in Figure 18, the response rate was substantially higher in eculizumab-treated patients (40.3%) than in placebo-treated patients (12.7%), showing a clinically significant response by both patient- and physician-assessed outcome measures in patients treated with eculizumab. With increasingly stringent response criteria, the superiority of response to eculizumab over placebo becomes more pronounced, with odds ratios exceeding 10.

Example 6: Efficacy of Eculizumab is Maintained Beyond 26 Weeks in Patients with AChR+ Refractory Generalized Myasthenia Gravis (gMG)

Patients who completed REGAIN were allowed to continue into an open-label extension study known as ECU-MG-302. Each patient enrolled in the extension trial underwent an initial 4-week blinded induction before receiving open-label eculizumab maintenance treatment (1200 mg every 2 weeks). MG-ADL, QMG, MGC, and MG-QOL15 scores and safety were assessed.

In contrast with Study ECU-MG-301, in which patients were required to maintain stable MG therapy throughout the 26-week study period, adjustment of background immunosuppressant therapy (IST), including corticosteroids and acetylcholinesterase inhibitors (AChI), was permitted in Study ECU-MG-302. Investigators could change dosing of an existing IST/AChI, discontinue an existing IST/AChI, or add a new IST/AChI.

The MG-ADL total score in eculizumab/eculizumab patients (n=56) was unchanged from open-label baseline through week 52. In the placebo/eculizumab patients (n=60), rapid improvement in MG-ADL total score from open-label baseline was demonstrated with a change from ECU-MG-302 baseline in MG-ADL total score observed as early as week 1 (-1.6 [-2.28, -0.89]; $p<0.0001$). The majority of the overall treatment effect was achieved by week 4 (-

2.4 [-3.19, -1.71]; p<0.0001) during the blind induction phase, and was sustained through week 52 (-2.7 [-3.73, -1.63]; p<0.0001). Changes in QMG, MGC, and MG-QOL15 total scores followed a pattern similar to that of the MG-ADL (QMG: –4.6; *P*<.0001; MGC: −5.1; *P*<.0001; and MG-QOL15: –5.7; *P*=.005 at week 52). Similar patterns of response were seen on the respiratory, bulbar, limb, and ocular MG-ADL domains. The safety profile of eculizumab remained unchanged throughout the open-label extension study and was consistent with the known profile.

Overall, 65 (55.6%) patients reported a change in their IST usage during the study. Greater proportions of patients had dose reductions or stopped ≥1 IST than those who had dose increases or started ≥1 IST (Table 26). 55 (47.0%) patients decreased their daily dose of 1 IST and 2 (1.7%) patients decreased the daily dose of >1 IST; 29 (24.8%) patients increased their daily dose of 1 IST, and none increased their dose of >1 IST. 19 (16.2%) patients stopped an existing IST; 5 (4.3%) patients started a new IST. The most common reason for change in IST therapy was improvement in MG symptoms, with 42 (35.9%) patients reporting improvement in MG symptoms as the reason for changing IST therapy. In comparison, 21 (17.9%) patients reported worsening of MG symptoms as the primary reason for changing IST therapy. Side-effects/intolerance to an IST was reported as the reason for change in IST therapy in 13 (11.1%) patients.

TABLE 26: SUMMARY OF CHANGES IN IMMUNOSUPPRESSANT THERAPY STATUS − EXTENSION SAFETY SET

	Placebo/Eculizumab (N = 61)		Eculizumab/Eculizumab (N = 56)		All Patients (N = 117)	
Parameter	**Change IST Events, n**	**Patients, n (%)**	**Change IST Events, n**	**Patients, n (%)**	**Change IST Events, n**	**Patients, n (%)**
IST Change Events and Patients with IST Changes	148	36 (59.0)	157	29 (51.8)	305	65 (55.6)
Changes Made in IST Status						
Start of New IST	2	2 (3.3)	5	3 (5.4)	7	5 (4.3)
Stop of an Existing IST	9	7 (11.5)	13	12 (21.4)	22	19 (16.2)
Increase the Daily dose of one IST	33	16 (26.2)	37	13 (23.2)	70	29 (24.8)
Decrease the Daily dose of one IST	102	30 (49.2)	102	25 (44.6)	204	55 (47.0)
Increased the Daily dose of more than one IST	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Decreased the Daily dose of more than one IST	2	2 (3.3)	0	0 (0.0)	2	2 (1.7)
Primary reason for change in IST Status						
MG symptoms improved	88	26 (42.6)	70	16 (28.6)	158	42 (35.9)
MG symptoms worsened	22	11 (18.0)	19	10 (17.9)	41	21 (17.9)
Side effects-intolerant to existing IST	12	6 (9.8)	15	7 (12.5)	27	13 (11.1)
New indication other than MG for IST usage	0	0 (0.0)	1	1 (1.8)	1	1 (0.9)
Other	26	11 (18.0)	51	12 (21.4)	77	23 (19.7)

Abbreviations: IST = immunosuppressant therapy; MG = myasthenia gravis

Overall, the extension study demonstrated that patients who received eculizumab in

Study ECU-MG-301 sustained their improvements through 52 weeks of additional eculizumab treatment in Study ECU-MG-302. For patients who received placebo in Study ECU-MG-301, an improvement occurred rapidly after starting eculizumab treatment and was maintained through 52 weeks of Study ECU-MG-302, similar to the effect observed in eculizumab-treated patients in Study ECU-MG-301.

TABLE 27: SEQUENCE SUMMARY

SEQ ID NO: 1 GYIFSNYWIQ
SEQ ID NO: 2 EILPGSGSTEYTENFKD
SEQ ID NO: 3 YFFGSSPNWYFDV
SEQ ID NO: 4 GASENIYGALN
SEQ ID NO: 5 GATNLAD
SEQ ID NO: 6 QNVLNTPLT
SEQ ID NO: 7 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFK DRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS
SEQ ID NO: 8 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIK
SEQ ID NO: 9 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG K
SEQ ID NO: 10 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFK DRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV

TCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 11 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
SEQ ID NO: 12 QVQLVQSGAEVKKPGASVKVSCKASGHIFSNYWIQWVRQAPGQGLEWMGEILPGSGHTEYTENFK DRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS
SEQ ID NO: 13 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVLHEALHSHYTQKSLSLSLG K
SEQ ID NO: 14 QVQLVQSGAEVKKPGASVKVSCKASGHIFSNYWIQWVRQAPGQGLEWMGEILPGSGHTEYTENFK DRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVLHEALHSHYTQKSLSLSLGK
SEQ ID NO: 15 ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVTSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTL YITREPEVTCVVVDVSHEDPEVQFNWYVDGMEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNG KEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K
SEQ ID NO: 16 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFK DRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVTS SNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLYITREPEV TCVVVDVSHEDPEVQFNWYVDGMEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVS NKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 17 GASENIYHALN

SEQ ID NO: 18 EILPGSGHTEYTENFKD
SEQ ID NO: 19 GHIFSNYWIQ
SEQ ID NO: 20 QVQLVQSGAEVKKPGASVKVSCKASGHIFSNYWIQWVRQAPGQGLEWMGEILPGSGHTEYTENFK DRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 21 SYAIS
SEQ ID NO: 22 GIGPFFGTANYAQKFQG
SEQ ID NO: 23 DTPYFDY
SEQ ID NO: 24 SGDSIPNYYVY
SEQ ID NO: 25 DDSNRPS
SEQ ID NO: 26 QSFDSSLNAEV
SEQ ID NO: 27 QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISVWRQAPGQGLEWMGGIGPFFGTANYAQKFQ GRVTITADESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSS
SEQ ID NO: 28 DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSN SGNTATLTISGTQAEDEADYYCQSFDSSLNAEVFGGGTKLTVL
SEQ ID NO: 29 NYIS
SEQ ID NO: 30 IIDPDDSYTEYSPSFQG
SEQ ID NO: 31 YEYGGFDI

SEQ ID NO: 32 SGDNIGNSYVH
SEQ ID NO: 33 KDNDRPS
SEQ ID NO: 34 GTYDIESYV
SEQ ID NO: 35 EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTEYSPSFQG QVTISADKSISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
SEQ ID NO: 36 SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSN SGNTATLTISGTQAEDEADYYCGTYDIESYVFGGGTKLTVL
SEQ ID NO: 37 QVQLVESGGGLVQPGRSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVGAIFTGSGAEYKAEWA KGRVTISKDTSKNQVVLTMTNMDPVDTATYYCASDAGYDYPTHAMHYWGQGTLVTVSS
SEQ ID NO: 38 DIQMTQSPSSLSASVGDRVTITCRASQGISSSLAWYQQKPGKAPKLLIYGASETESGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQNTKVGSSYGNTFGGGTKVEIK
SEQ ID NO: 39 QVQLVESGGGLVQPGRSLRLSCAASGFTVHSSYYMAWVRQAPGKGLEWVGAIFTGSGAEY KAEWAKGRVTISKDTSKNQVVLTMTNMDPVDTATYYCASDAGYDYPTHAMHYWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL RRGPKVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVLHEALHAHYTRKELSLSP

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CLAIMS

What is claimed is:

1. A method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering a therapeutically effective amount of eculizumab to the patient;

wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability; and

wherein the patient is administered eculizumab for at least 26 weeks.

2. The method of claim 1, wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg of eculizumab as a fifth induction dose on day 28; and

wherein the patient is administered eculizumab for at least 26 weeks.

3. The method of claim 2, wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter.

4. The method of claim 3, further comprising performing plasmapheresis on the patient and administering eculizumab at a dose of between 300 mg and 1200 mg to the patient within 4 hours of completion of plasmapheresis.

5. The method of claim 3, further comprising performing plasmapheresis on the patient and administering eculizumab at a dose of between 600 mg and 900 mg to the patient within 90 minutes of completion of plasmapheresis.

6. The method of claim 3, further comprising performing plasmapheresis on the patient and administering eculizumab at a dose of 600 mg to the patient within 1 hour of

completion of plasmapheresis.

7. The method of claim 1, wherein the patient experiences a clinically meaningful improvement (reduction) in Myasthenia Gravis Activities of Daily Living (MG-ADL) score after 26 weeks of treatment.

8. The method of claim 7, wherein the clinically meaningful improvement the patient experiences is at least a 3 point reduction in the patient's MG-ADL score after 26 weeks of treatment.

9. The method of claim 1, wherein the patient experiences a clinically meaningful improvement (reduction) in quantitative Myasthenia Gravis score (QMG) after 26 weeks of treatment.

10. The method of claim 9, wherein the clinically meaningful improvement the patient experiences is at least a 4 point reduction in the patient's QMG score after 26 weeks of treatment.

11. The method of claim 1, wherein the patient experiences a clinically meaningful improvement (reduction) in Myasthenia Gravis Composite (MGC) score after 26 weeks of treatment.

12. The method of claim 11, wherein the clinically meaningful improvement the patient experiences is at least a 6 point reduction in the patient's MGC score after 26 weeks of treatment.

13. The method of claim 1, wherein the patient experiences a clinically meaningful improvement (reduction) in quality of life as measured by Myasthenia Gravis Quality of Life (MG-QOL-15) score after 26 weeks of treatment.

14. The method of claim 13, wherein the clinically meaningful improvement the patient experiences is at least a 6 point reduction in the patient's MG-QOL-15 score after 26 weeks of treatment.

15. The method of claim 1, wherein the patient experiences a clinically meaningful improvement (reduction) in neuro-fatigue as measured by Neuro-QOL Fatigue score after 26 weeks of treatment.

16. The method of claim 15, wherein the clinically meaningful improvement the patient experiences is at least an 8 point reduction in the patient's Neuro-QOL score after 26 weeks of treatment.

17. The method of claim 1, wherein the patient experiences a clinically meaningful improvement (increase) in health status as measured by EQ-5D health status score after 26 weeks of treatment.

18. A method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient;

wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability;

wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg of eculizumab as a fifth induction dose on day 28;

wherein the patient is administered eculizumab for at least 26 weeks;

wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter; and

wherein the patient has a clinically meaningful improvement (reduction) in at least two measurements of generalized myasthenia gravis severity selected from the group consisting of MG-ADL, QMG, MGC, MG-QOL, and Neuro-QOL.

19. A method of treating refractory generalized myasthenia gravis in a patient in need

thereof comprising administering eculizumab to the patient;

wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability;

wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg of eculizumab as a fifth induction dose on day 28;

wherein the patient is administered eculizumab for at least 26 weeks;

wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter; and

wherein the patient has a clinically meaningful improvement (reduction) in five measurements of generalized myasthenia gravis severity, wherein the five measurements of generalized myasthenia gravis severity are a reduction in MG-ADL of at least 3 points, a reduction of QMG of at least 4 points, a reduction in MGC of at least 6 points, a reduction in MG-QOL of at least 6 points, and a reduction in Neuro-QOL of at least 8 points.

20. The method of claim 19, wherein the patient has a clinically meaningful improvement (reduction) in five measurements of generalized myasthenia gravis, wherein the five measurements of generalized myasthenia gravis severity are a reduction in MG-ADL of at least 4 points, a reduction of QMG of at least 5 points, a reduction in MGC of at least 10 points, a reduction in MG-QOL of at least 11 points, and a reduction in Neuro-QOL of at least 16 points.

21. The method of claim 1, wherein eculizumab is administered by intravenous infusion.

22. The method of claim 1, wherein eculizumab is administered subcutaneously.

23. The method of claim 1, wherein the eculizumab comprises a heavy chain amino acid sequence according to SEQ ID NO: 10 and a light chain amino acid sequence according to

SEQ ID NO: 11.

24. The method of claim 1, wherein the eculizumab is an eculizumab variant comprising a heavy chain amino acid sequence according to SEQ ID NO: 14 and a light chain amino acid sequence according to SEQ ID NO: 11.

25. The method of claim 1, wherein the patient has failed treatment over one year or more with two or more ISTs in sequence or in combination.

26. The method of claim 1, wherein the patient has failed at least one IST and requires chronic plasma exchange or IVIg to control symptoms.

27. The method of claim 1, wherein the therapeutically effective amount of eculizumab is maintained at a concentration of between 50-100 μg/mL in the patient's serum.

28. The method of claim 1, wherein the patient experiences a reduction in the administration of one or more IST following at least 26 weeks of treatment.

29. The method of claim 1, wherein the patient experiences a reduction in IST dosing following at least 26 weeks of treatment.

30. The method of claim 1, wherein the patient experiences a reduction in one or more IST dosing and a discontinuation in one or more IST following at least 26 of treatment.

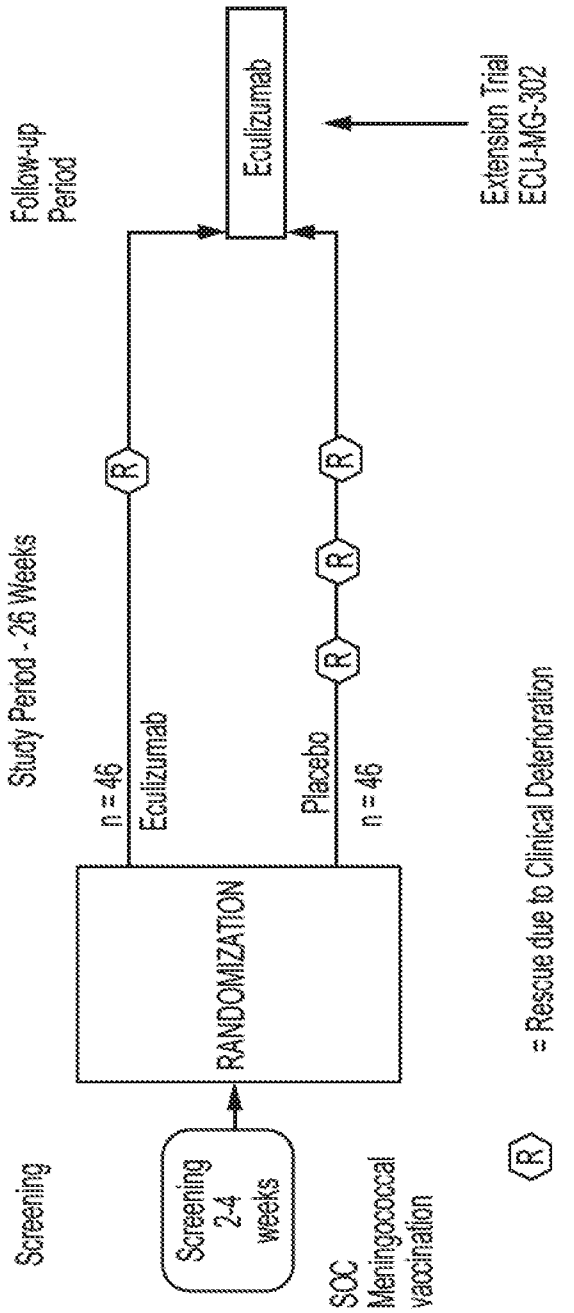

Screening
Screening 2-4 weeks
SOC Meningococcal vaccination
RANDOMIZATION
n = 46
Eculizumab
Placebo
n = 46
Study Period - 26 Weeks
R
Follow-up Period
Eculizumab
Extension Trial ECU-MG-302
= Rescue due to Clinical Deterioration
Rescue therapy is permitted if a subject experiences Clinical Deterioration as defined by the protocol. Subject can remain in the trial.

Fig. 1

EUROQOL (EQ-5D) HEALTH QUESTIONAIRE

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

Fig. 2A

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion.

Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

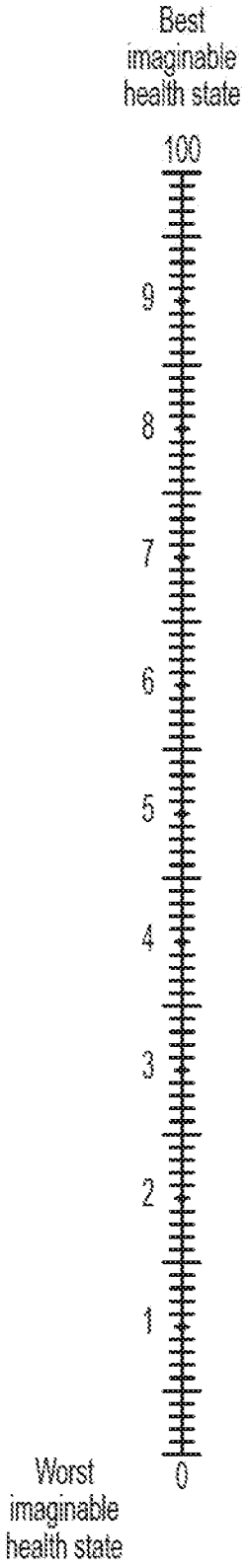


Fig. 2B

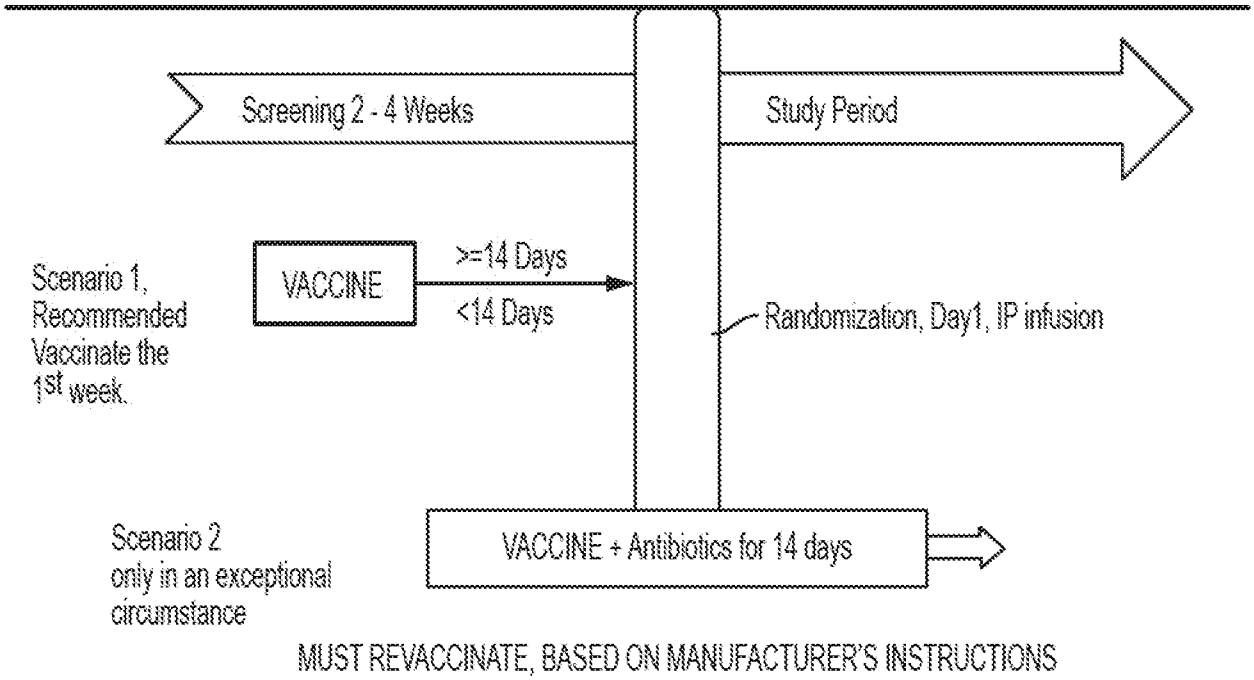

Screening 2 - 4 Weeks
Study Period
Scenario 1,
Recommended
Vaccinate the
1st week.
VACCINE
>=14 Days
<14 Days
Randomization, Day1, IP infusion
Scenario 2
only in an exceptional
circumstance
VACCINE + Antibiotics for 14 days
MUST REVACCINATE, BASED ON MANUFACTURER'S INSTRUCTIONS

Fig. 3

- Eculizumab or placebo IV infusion over ~ 35 mins

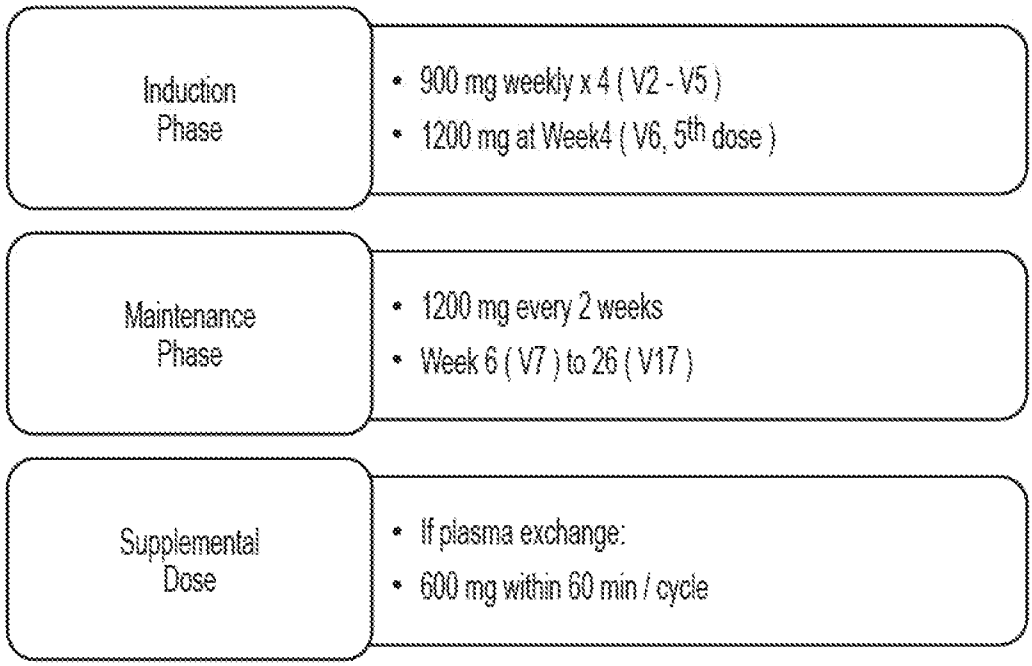


Fig. 4

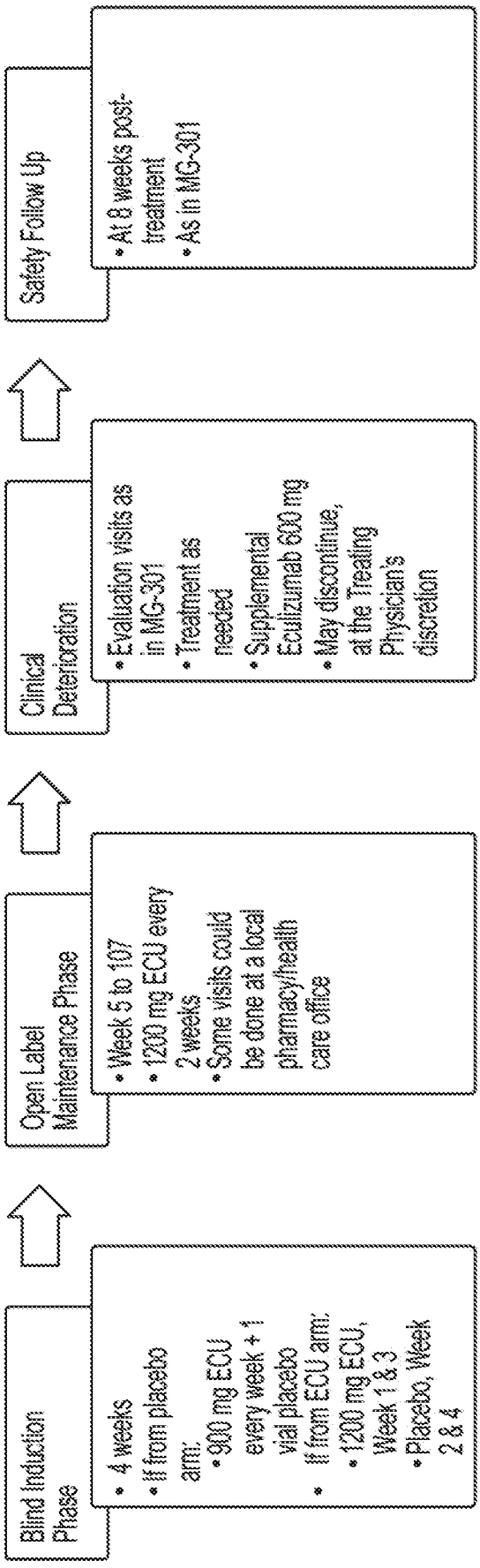

Blind Induction Phase
• 4 weeks
• If from placebo arm:
• 900 mg ECU every week + 1 vial placebo
• If from ECU arm:
• 1200 mg ECU, Week 1 & 3
• Placebo, Week 2 & 4
Open Label Maintenance Phase
• Week 5 to 107
• 1200 mg ECU every 2 weeks
• Some visits could be done at a local pharmacy/health care office
Clinical Deterioration
• Evaluation visits as in MG-301
• Treatment as needed
• Supplemental Eculizumab 600 mg
• May discontinue, at the Treating Physician's discretion
Safety Follow Up
• At 8 weeks post-treatment
• As in MG-301

Fig. 5

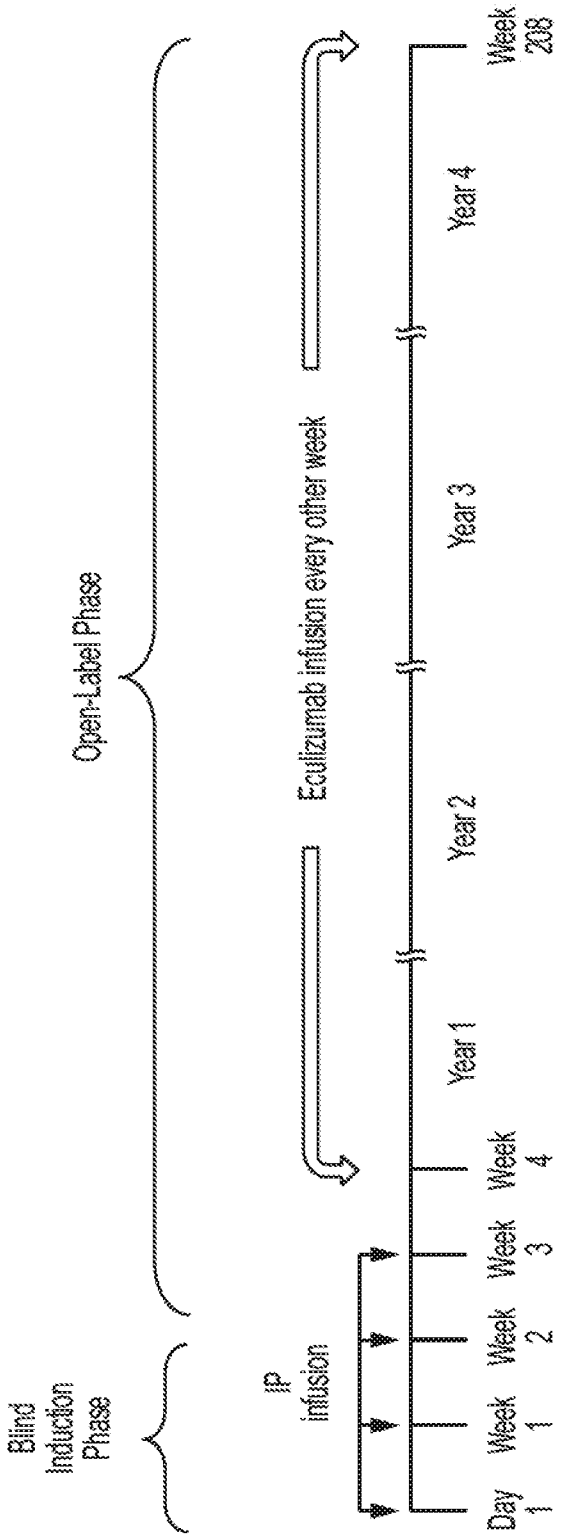

Blind Induction Phase
Open-Label Phase
IP infusion
Day 1
Week 1
Week 2
Week 3
Week 4
Eculizumab infusion every other week
Year 1
Year 2
Year 3
Year 4
Week 208

Fig. 6

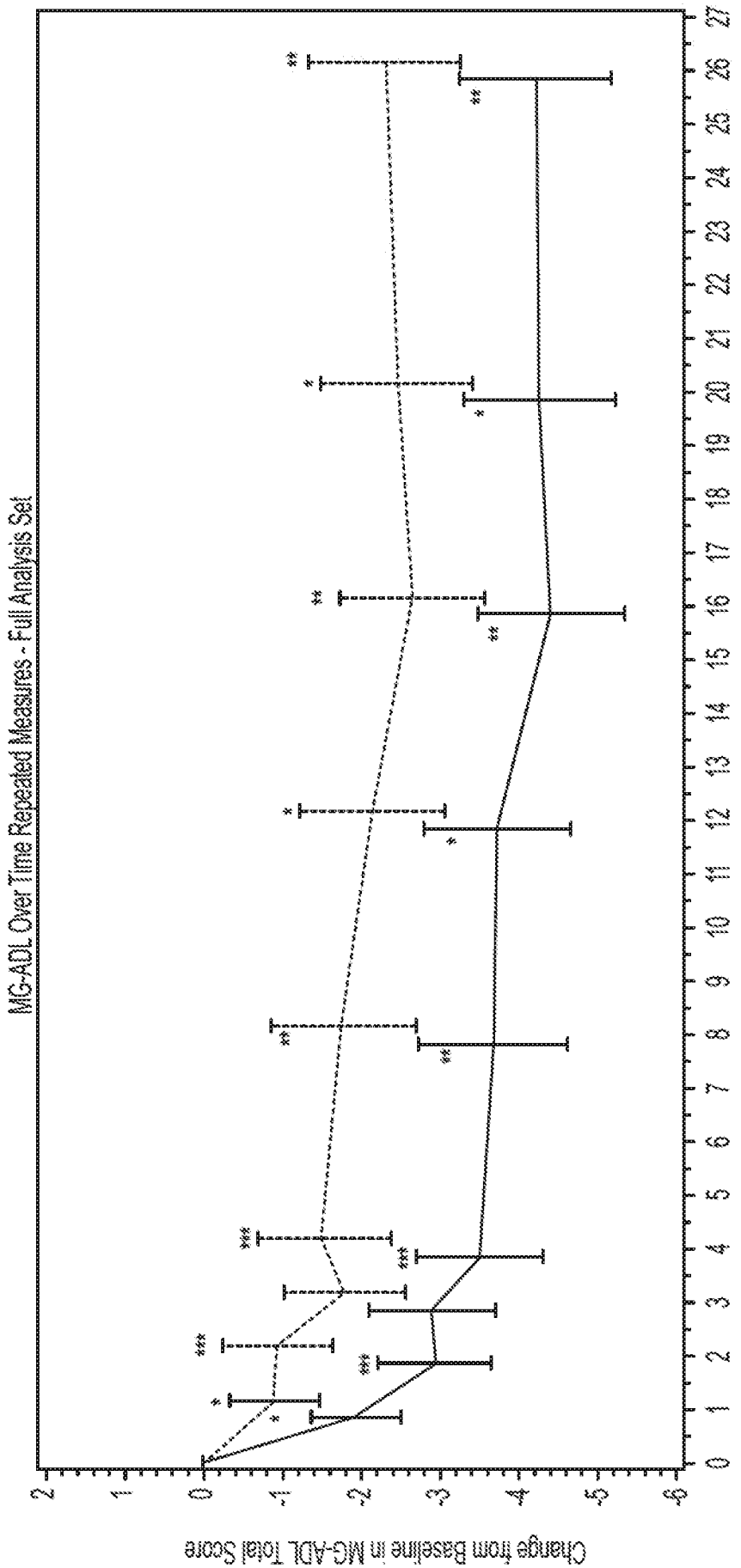

MG-ADL Over Time Repeated Measures - Full Analysis Set
Change from Baseline in MG-ADL Total Score
Weeks
Planned treatment
Eculizumab
Placebo
The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, and the MG-ADL total score at baseline. Missing MG-ADL total score values were not imputed.
*, **, and *** represent the statistical significance at two-sided alpha levels of 0.05, 0.01, and 0.001, respectively.

Fig. 7

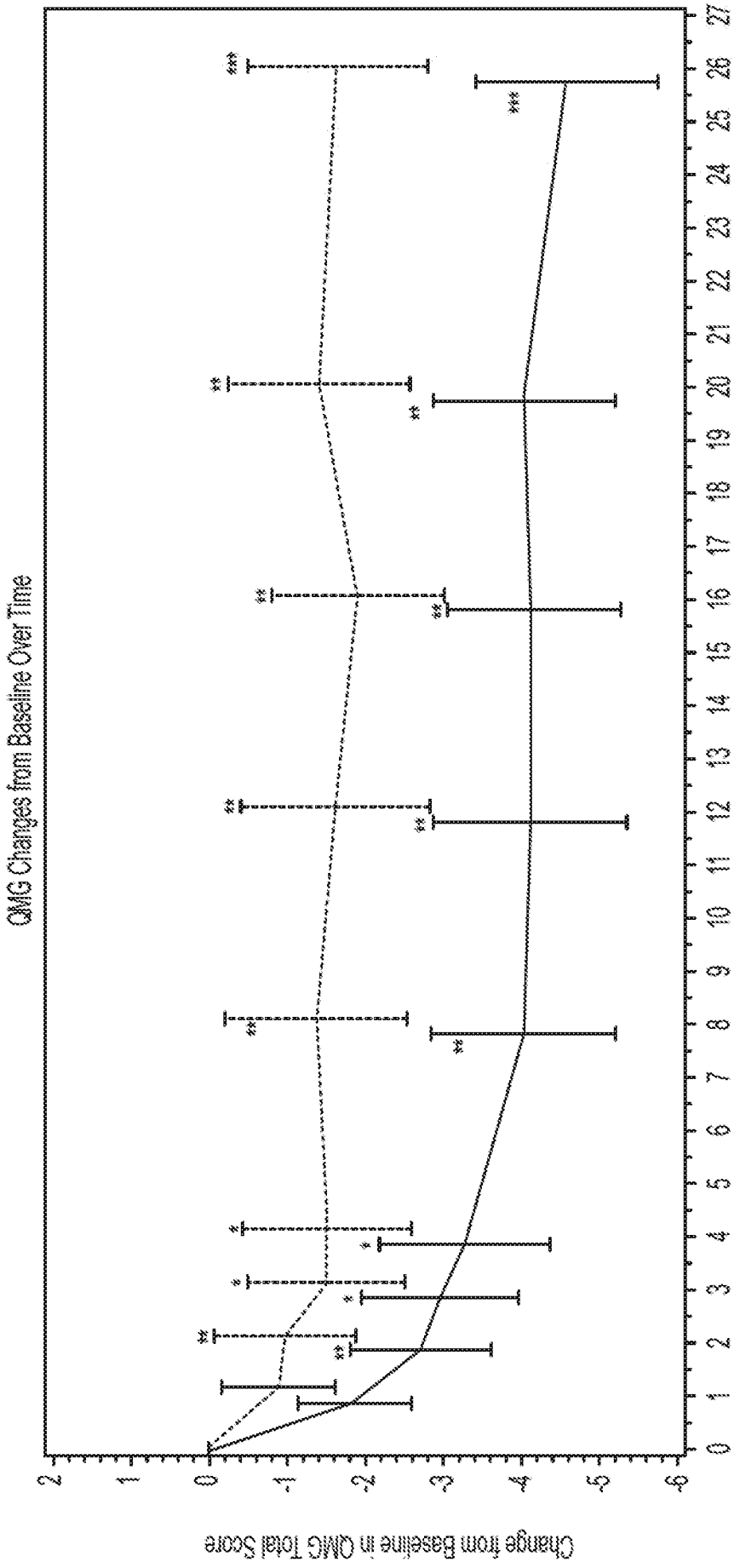
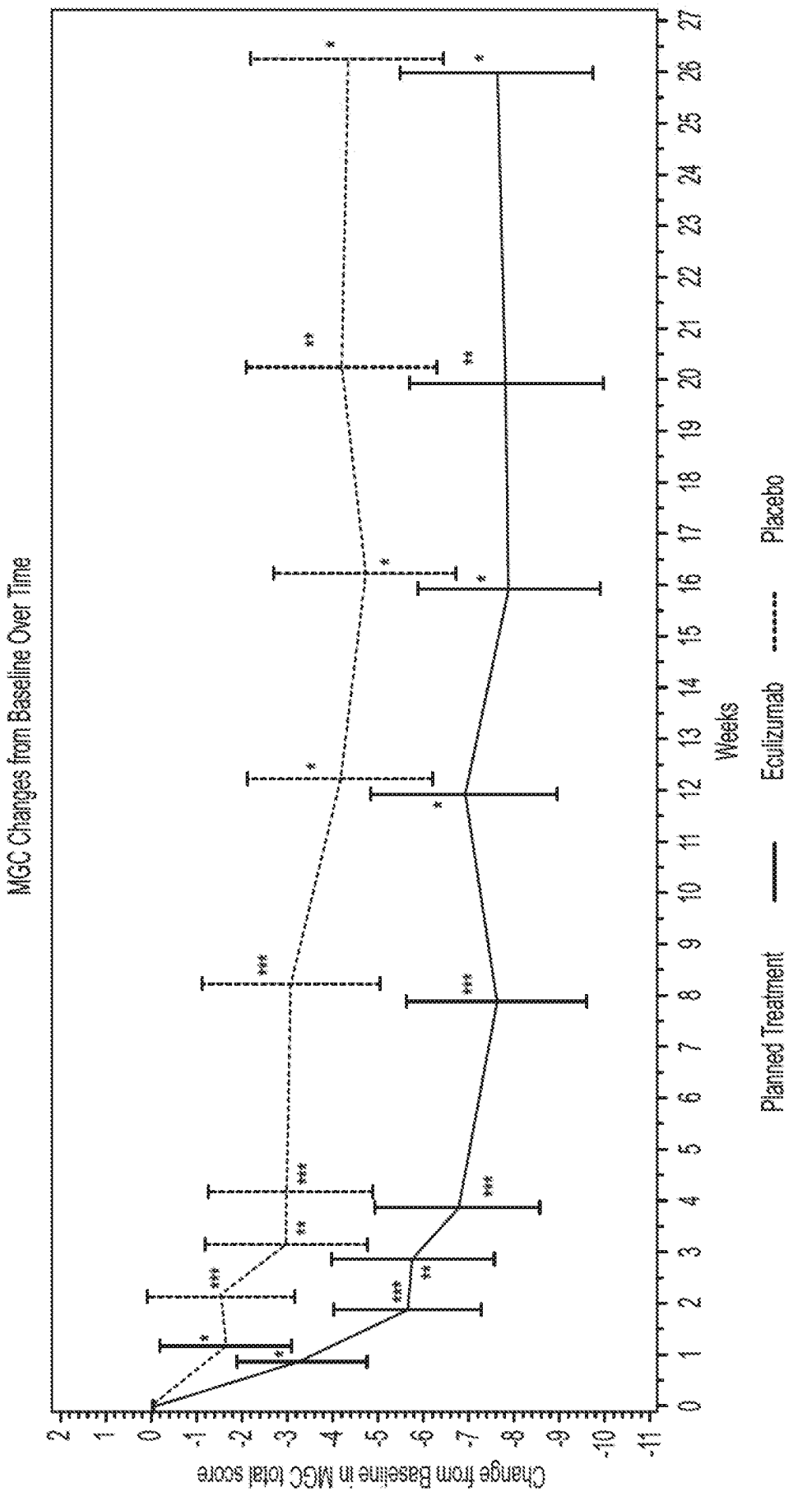

QMG Changes from Baseline Over Time
Change from Baseline in QMG Total Score
2
1
0
-1
-2
-3
-4
-5
-6
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
Weeks
Planned Treatment —— Eculizumab ------ Placebo
The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, and the QMG total score at baseline. Missing QMG total score values were not imputed.
*, **, and *** represent the statistical significance at two-sided alpha levels of 0.05, 0.01, and 0.001, respectively.

Fig. 8



The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, and the MGC total score at baseline. Missing MGC total score values were not imputed.
*, **, and *** represent the statistical significance at two-sided alpha levels of 0.05, 0.01, and 0.001, respectively.

Fig. 9

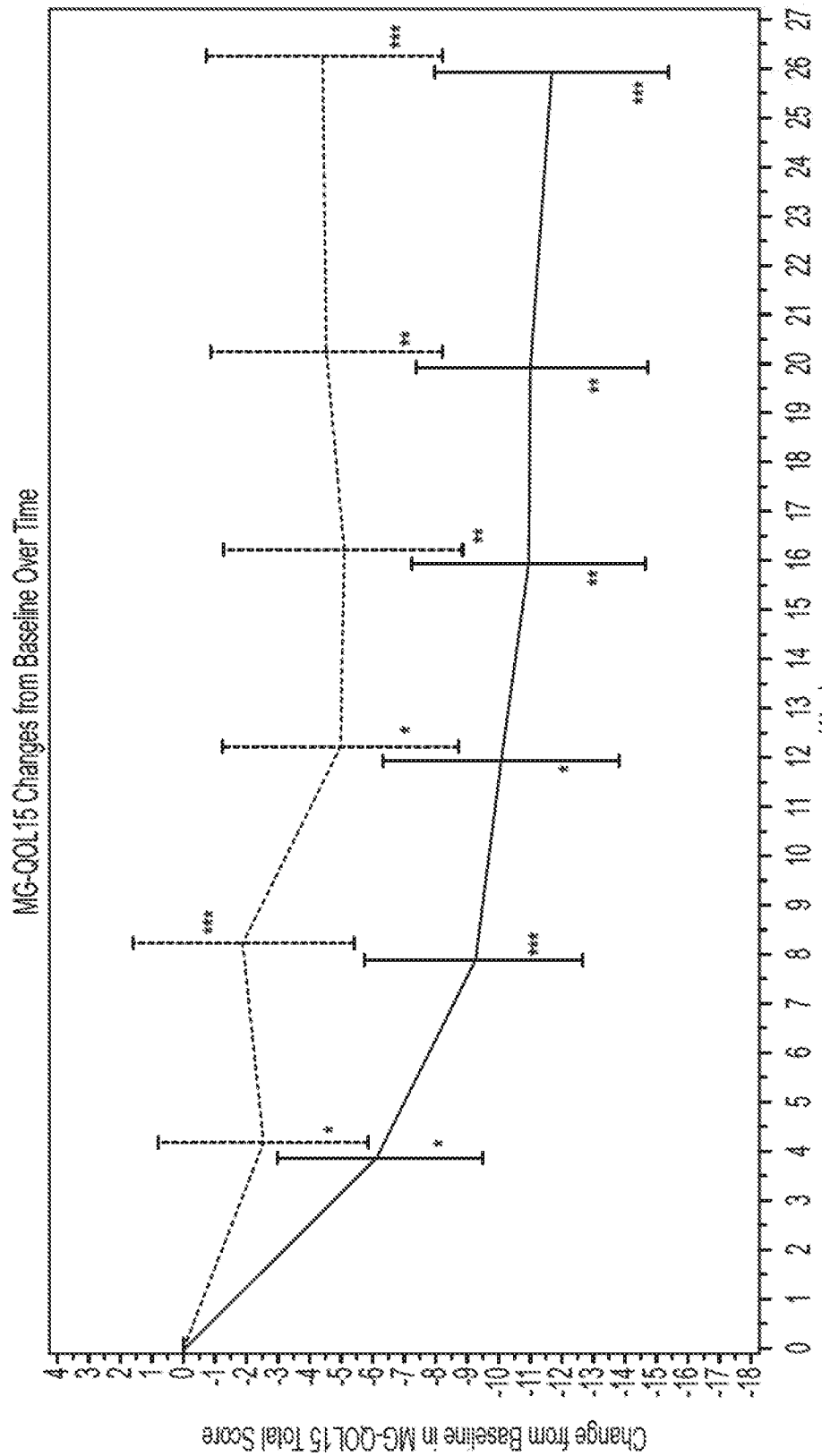

MG-QOL15 Changes from Baseline Over Time
Change from Baseline in MG-QOL15 Total Score
Weeks
Planned Treatment
Eculizumab
Placebo
The model included the following terms: treatment, visit, the treatment by visit interaction term, the MGFA randomization stratification variable, and the MG-QOL15 total score at baseline. Missing MG-QOL15 total score values were not imputed. *, **, and *** represent the statistical significance at two-sided alpha levels of 0.05, 0.01, and 0.001, respectively.

Fig. 10

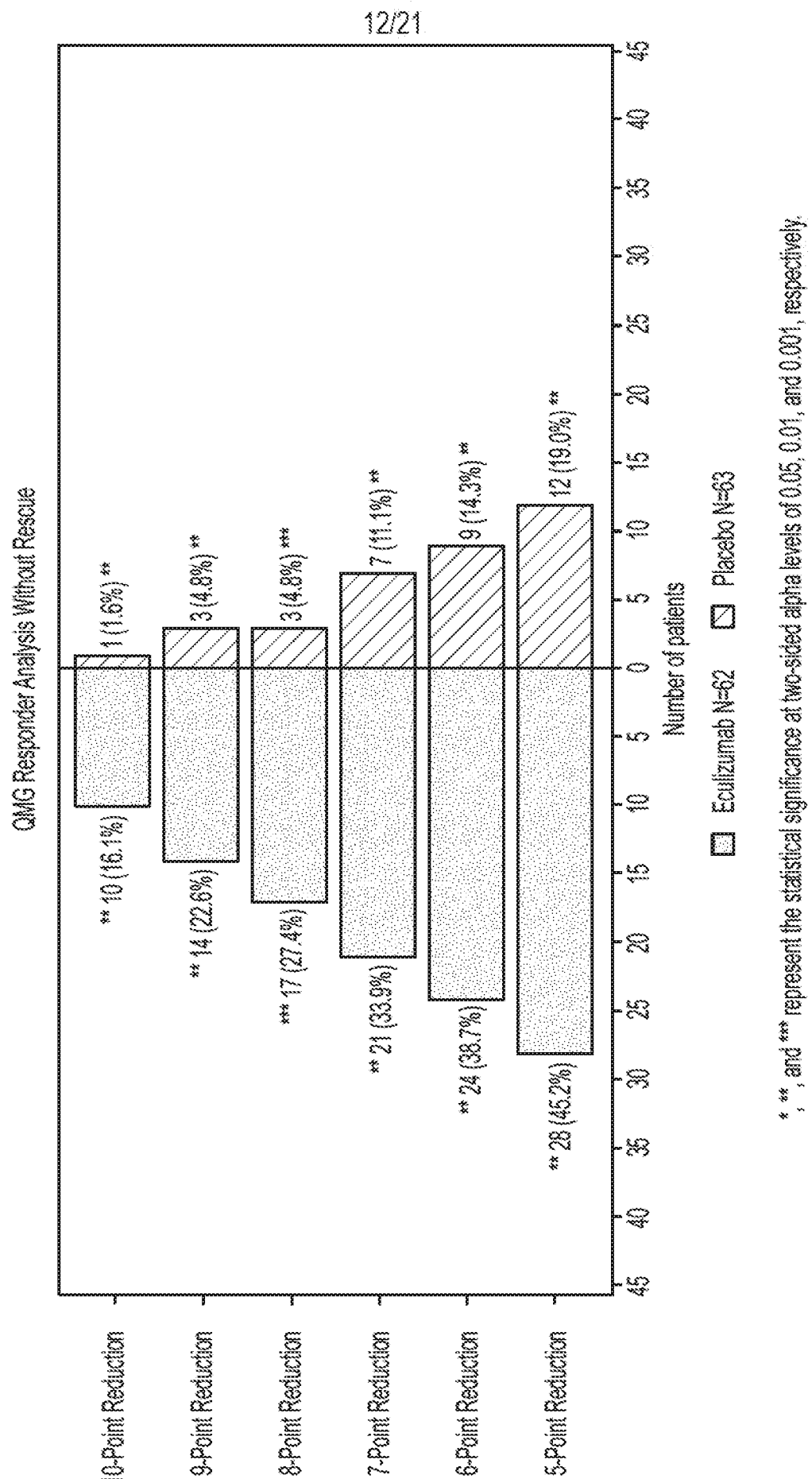

QMG Responder Analysis Without Rescue
10-Point Reduction
9-Point Reduction
8-Point Reduction
7-Point Reduction
6-Point Reduction
5-Point Reduction
** 10 (16.1%)
1 (1.6%) **
** 14 (22.6%)
3 (4.8%) **
*** 17 (27.4%)
3 (4.8%) ***
** 21 (33.9%)
7 (11.1%) **
** 24 (38.7%)
9 (14.3%) **
** 28 (45.2%)
12 (19.0%) **
45 40 35 30 25 20 15 10 5 0 5 10 15 20 25 30 35 40 45
Number of patients
Eculizumab N=62
Placebo N=63
*, **, and *** represent the statistical significance at two-sided alpha levels of 0.05, 0.01, and 0.001, respectively.

Fig. 11

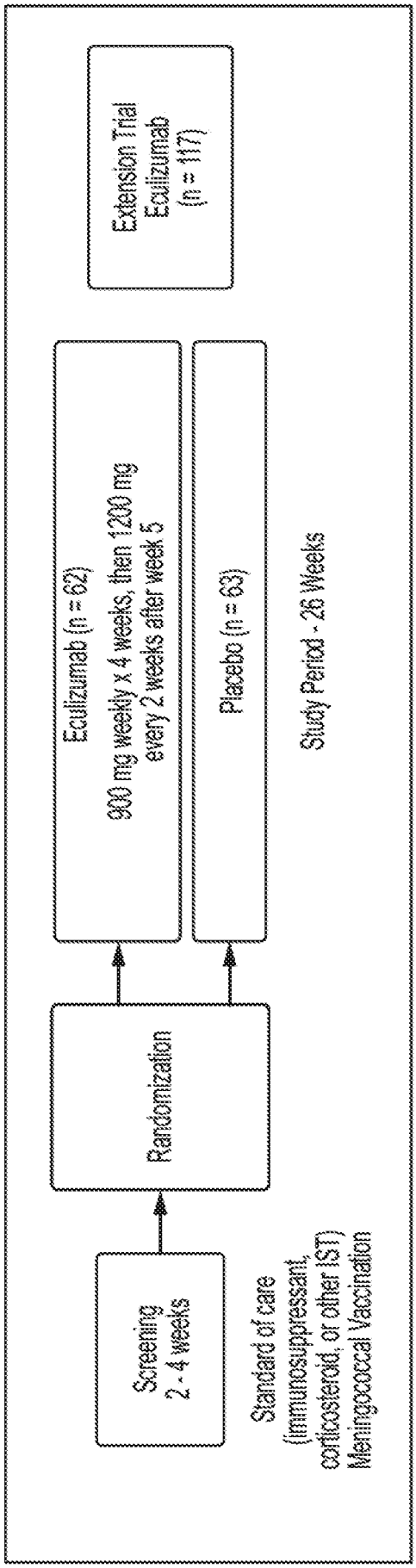

Extension Trial
Eculizumab
(n = 117)
Eculizumab (n = 62)
900 mg weekly x 4 weeks, then 1200 mg
every 2 weeks after week 5
Placebo (n = 63)
Study Period - 26 Weeks
Randomization
Screening
2 - 4 weeks
Standard of care
(immunosuppressant,
corticosteroid, or other IST)
Meningococcal Vaccination

Fig. 12

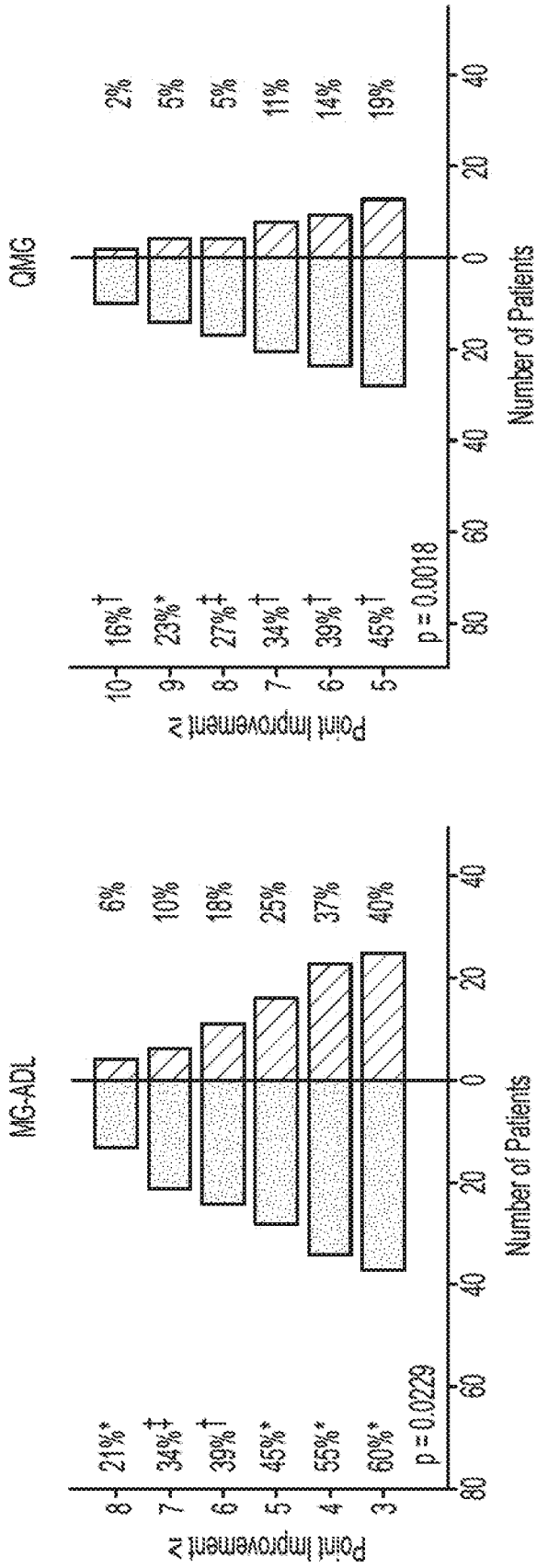

MG-ADL
QMG
Point improvement ≥
Number of Patients
21%*
34%†
39%†
45%*
55%*
60%*
6%
10%
18%
25%
37%
40%
16%†
23%*
27%†
34%†
39%†
45%†
2%
5%
5%
11%
14%
19%
p = 0.0229
p = 0.0018
ECULIZUMAB (n = 62)
PLACEBO (n = 63)
*p ≤ 0.05; †p ≤ 0.01; ‡p ≤ 0.001
MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis.

Fig. 13

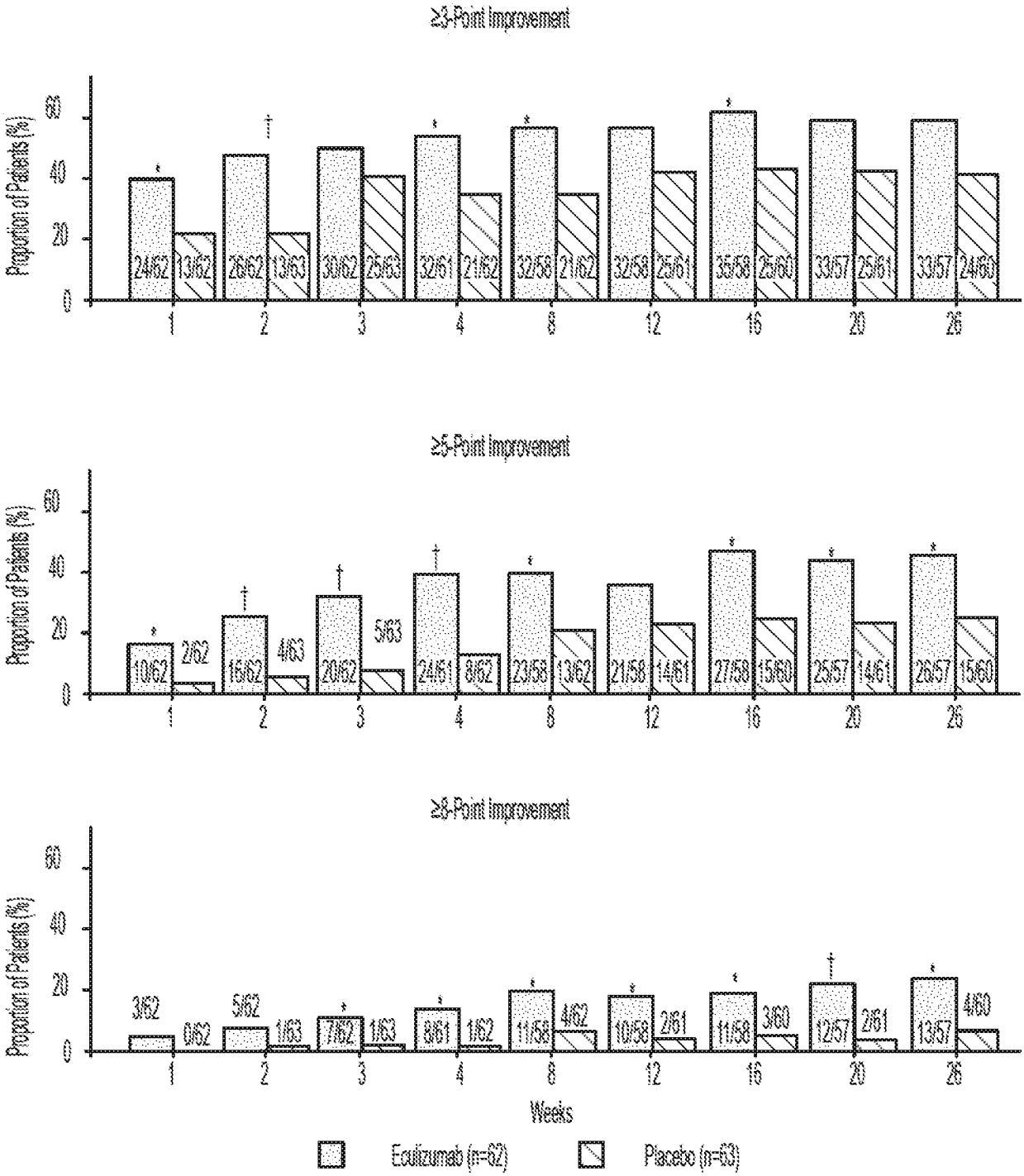

≥3-Point Improvement
Proportion of Patients (%)
0
20
40
60
24/62
13/62
28/62
13/63
30/62
25/63
32/61
21/62
32/58
21/62
32/58
25/61
35/58
25/60
33/57
25/61
33/57
24/60
1
2
3
4
8
12
16
20
26
≥5-Point Improvement
Proportion of Patients (%)
10/62
2/62
16/62
4/63
20/62
5/63
24/61
8/62
23/58
13/62
21/58
14/61
27/58
15/60
25/57
14/61
26/57
15/60
≥8-Point Improvement
Proportion of Patients (%)
3/62
0/62
5/62
1/63
7/62
1/63
8/61
1/62
11/58
4/62
10/58
2/61
11/58
3/60
12/57
2/61
13/57
4/60
Weeks
Ecallzumab (n=62)
Placebo (n=63)

Fig. 14

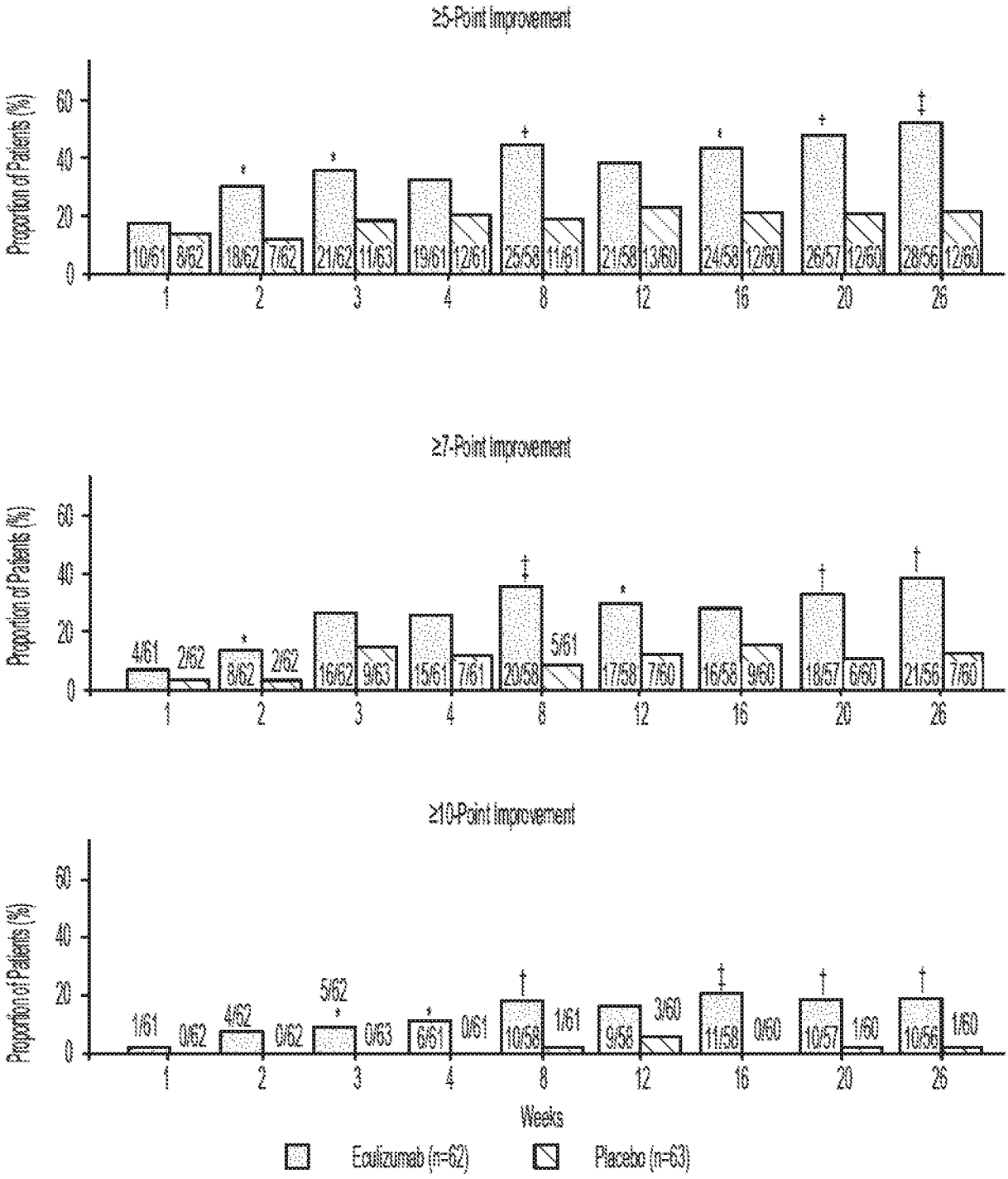
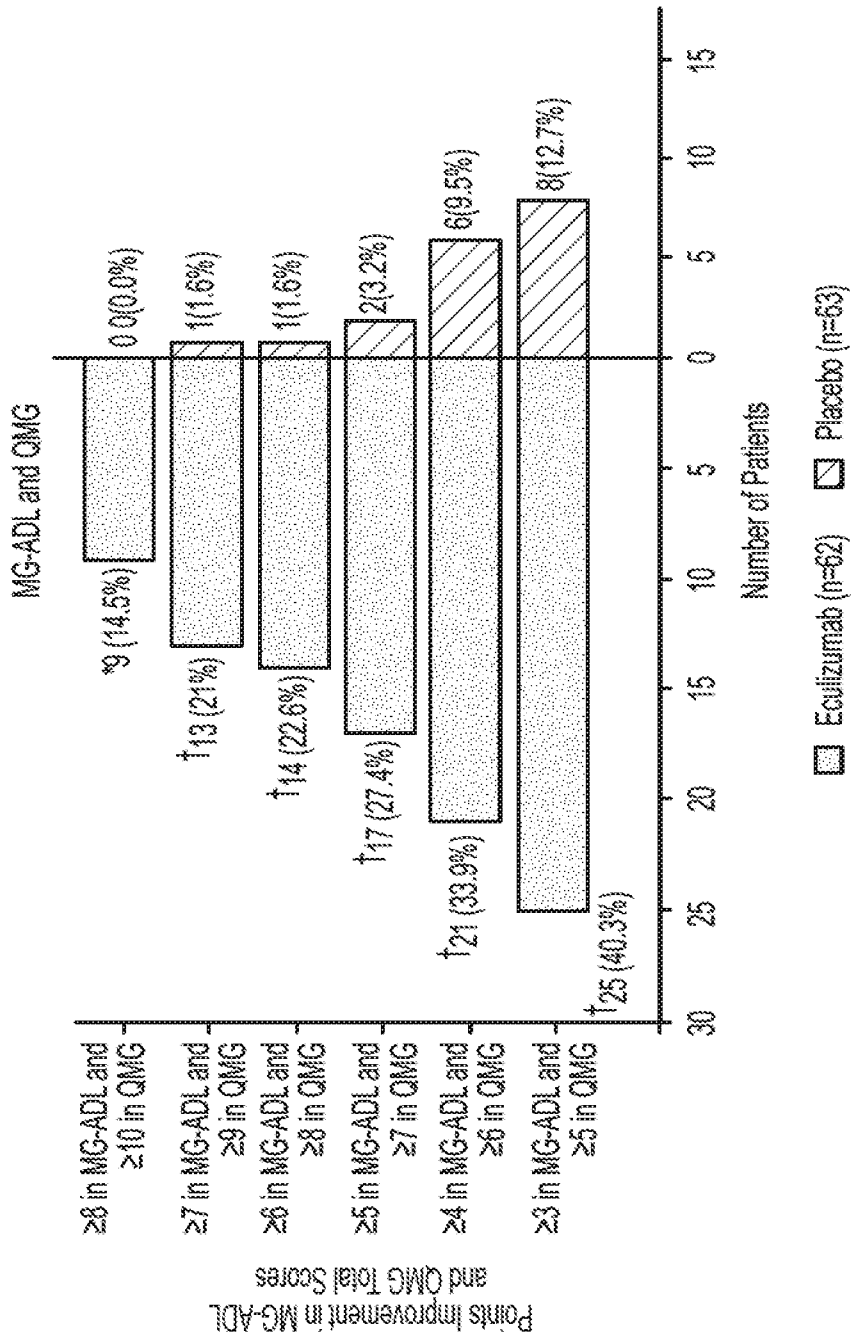

≥5-Point Improvement
Proportion of Patients (%)
0
20
40
60
10/61
6/62
18/62
7/62
21/62
11/63
19/61
12/61
25/58
11/61
21/58
13/60
24/58
12/60
26/57
12/60
28/56
12/60
1
2
3
4
8
12
16
20
26
≥7-Point Improvement
Proportion of Patients (%)
4/61
2/62
8/62
2/62
16/62
9/63
15/61
7/61
20/58
5/61
17/58
7/60
16/58
9/60
18/57
6/60
21/56
7/60
≥10-Point Improvement
Proportion of Patients (%)
1/61
0/62
4/62
0/62
5/62
0/63
3/61
0/61
10/58
1/61
9/58
3/60
11/58
0/60
10/57
1/60
10/56
1/60
Weeks
Evolocumab (n=62)
Placebo (n=63)

Fig. 15



*p ≤ 0.01; †p ≤ 0.001
MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis.

Fig. 16

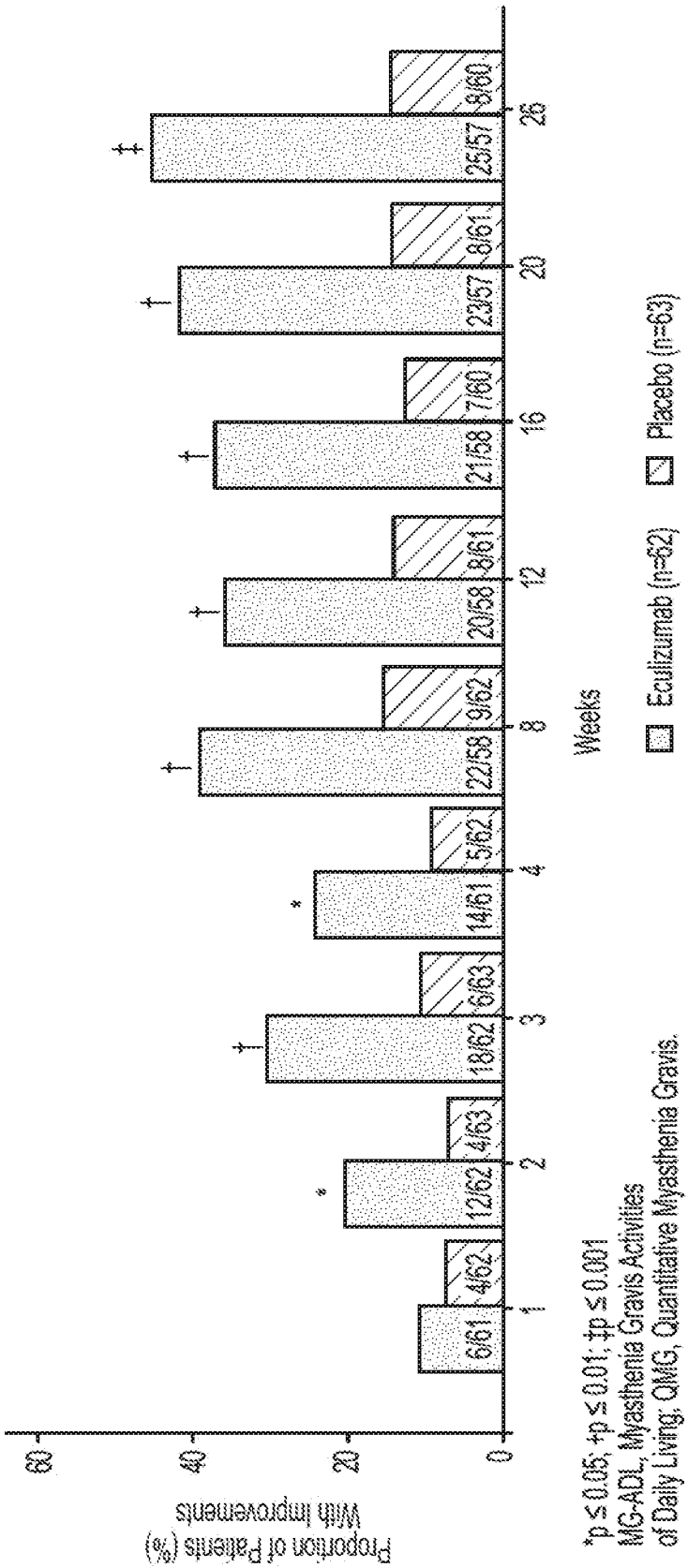

Improvements of ≥3 Points in MG-ADL Total Score and ≥5 Points in QMG Total Score
Proportion of Patients (%) With Improvements
0
20
40
60
6/61
4/62
12/62
4/63
18/62
6/63
14/61
5/62
22/58
9/62
20/58
8/61
21/58
7/60
23/57
8/61
25/57
8/60
1
2
3
4
8
12
16
20
26
Weeks
Eculizumab (n=62)
Placebo (n=63)
*p ≤ 0.05; †p ≤ 0.01; ‡p ≤ 0.001
MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis.

Fig. 17

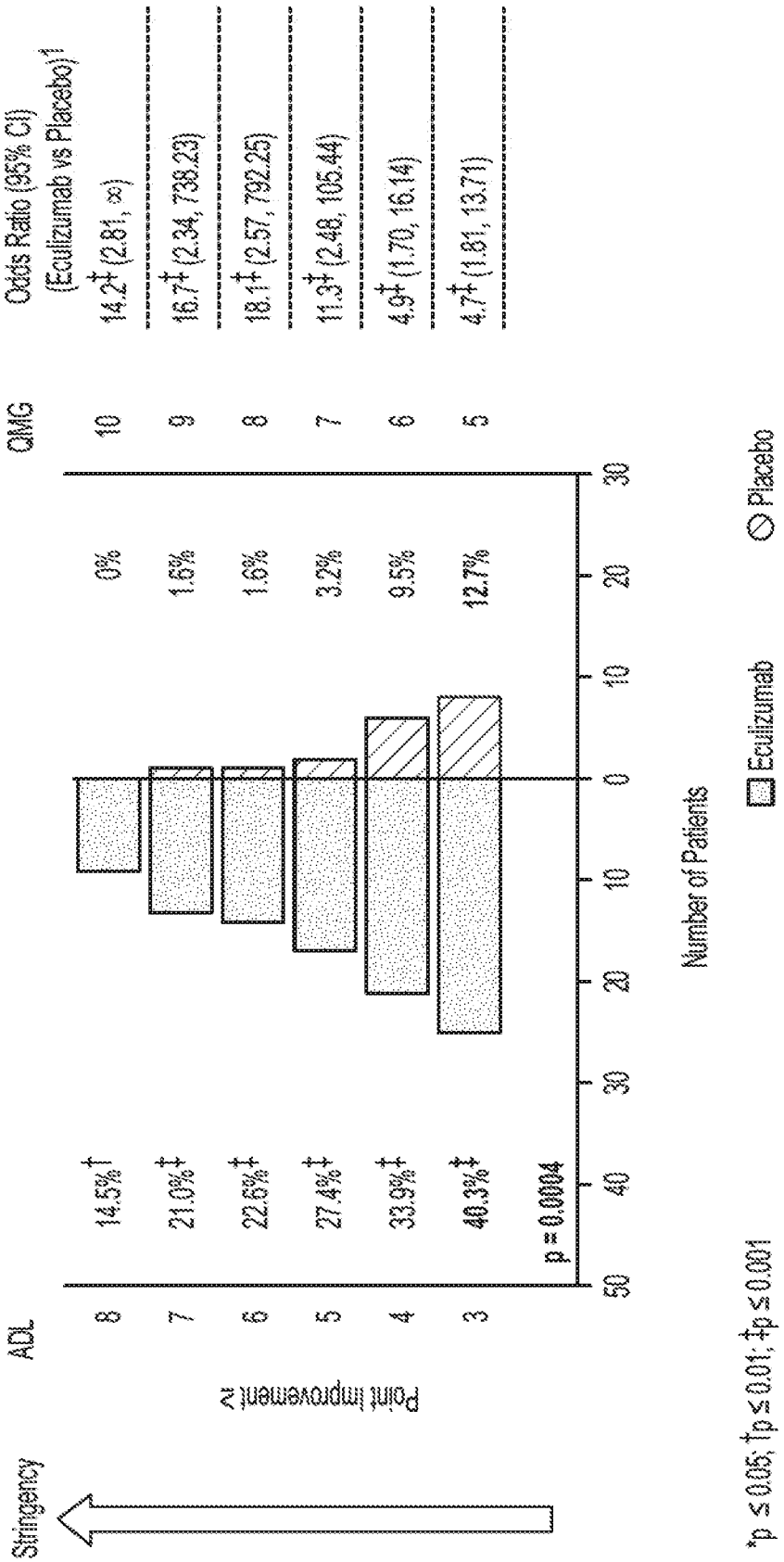

Stringency
ADL
QMG
Odds Ratio (95% CI)
(Eculizumab vs Placebo)[1]
8
7
6
5
4
3
14.5%†
21.0%‡
22.6%‡
27.4%‡
33.9%‡
40.3%‡
0%
1.6%
1.6%
3.2%
9.5%
12.7%
10
9
8
7
6
5
14.2† (2.81, ∞)
16.7† (2.34, 738.23)
18.1† (2.57, 792.25)
11.3† (2.48, 105.44)
4.9† (1.70, 16.14)
4.7† (1.81, 13.71)
p = 0.0004
50 40 30 20 10 0 10 20 30
Point improvement ≥
Number of Patients
Eculizumab
Placebo
*p ≤ 0.05; †p ≤ 0.01; ‡p ≤ 0.001

Fig. 18

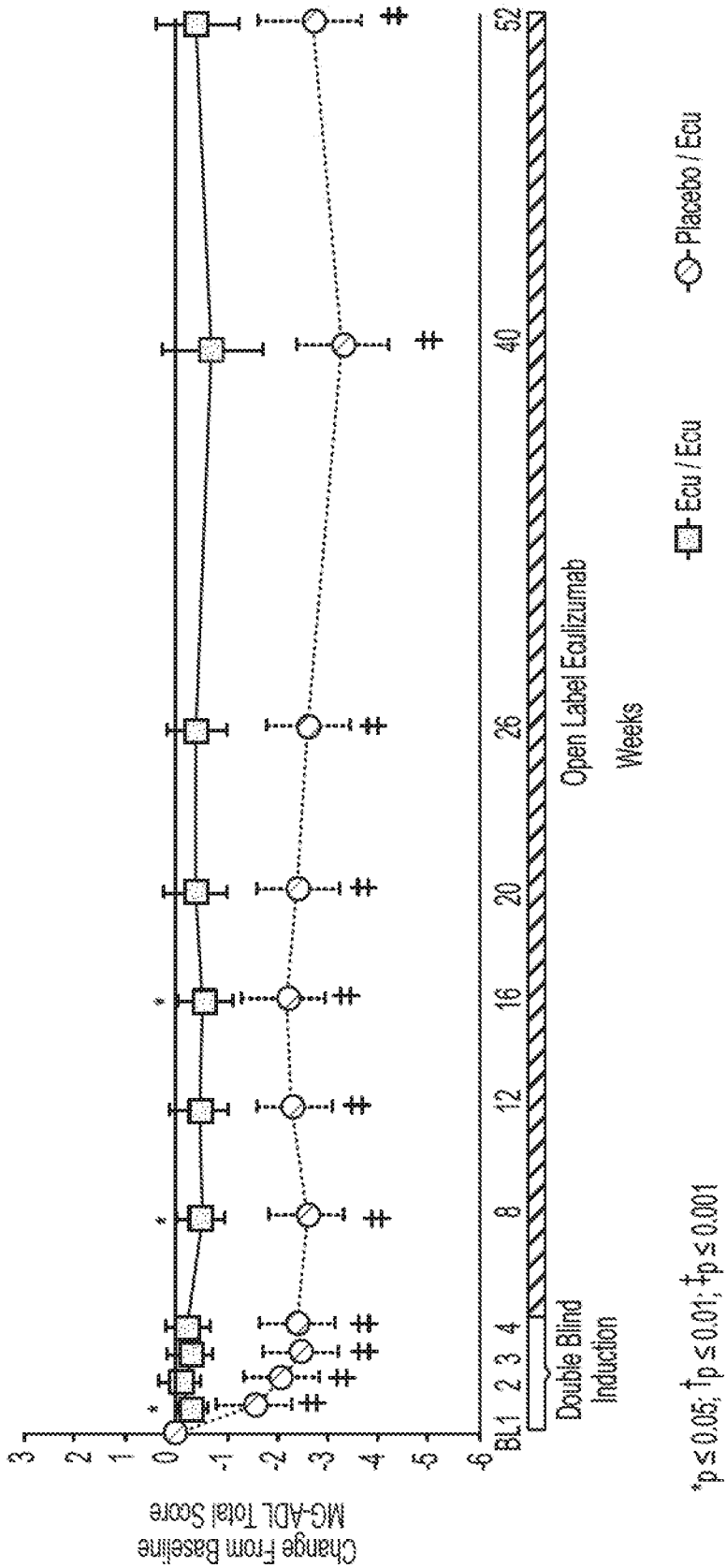

Change From Baseline
MG-ADL Total Score
3
2
1
0
-1
-2
-3
-4
-5
-6
BL 1 2 3 4 8 12 16 20 26 40 52
Double Blind Induction
Open Label Eculizumab
Weeks
Ecu / Ecu
Placebo / Ecu
*p ≤ 0.05; †p ≤ 0.01; ‡p ≤ 0.001

Fig. 19

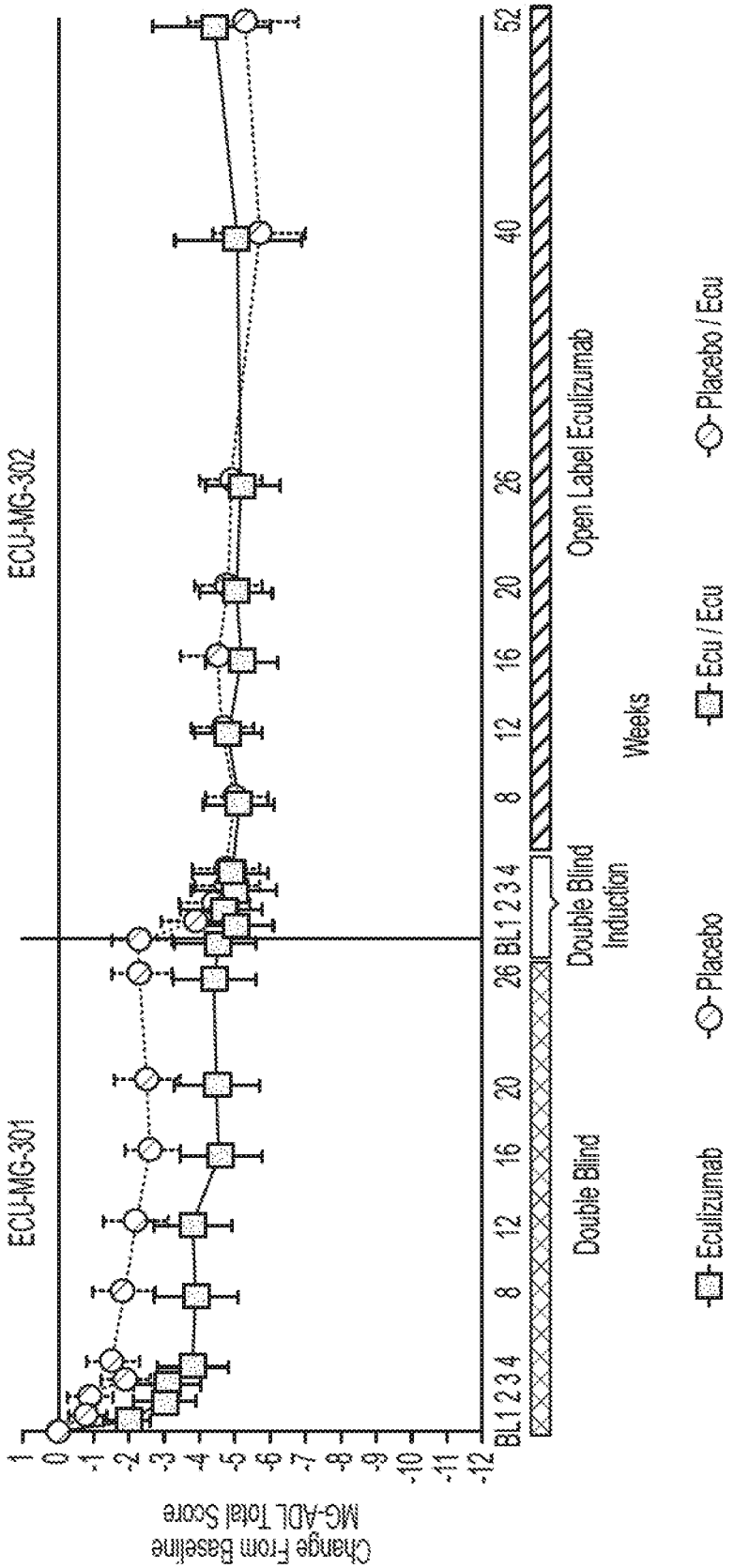

ECU-MG-302
ECU-MG-301
Change From Baseline
MG-ADL Total Score
1
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-11
-12
BL 1 2 3 4 8 12 16 20 26 BL 1 2 3 4 8 12 16 20 26 40 52
Weeks
Double Blind
Double Blind
Induction
Open Label Eculizumab
Eculizumab
Placebo
Ecu / Ecu
Placebo / Ecu

Fig. 20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/32767

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 39/395; A61P 21/04; C07K 16/28, 16/46, 16/18 (2017.01)
CPC - A61K 39/39566; C07K 16/28, 16/461, 16/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	(NATIONAL INSTITUTE OF HEALTH RESEARCH) Eculizumab (Soliris) for Refractory Myasthenia Gravis. March 2016 [retrieved on 02 October, 2017]. Pages 1-7; page 2, paragraph 2; page 4, paragraph 6; page 5, table 1; retrieved from the internet <https://www.euroscan.org/technologies/eculizumab-soliris-for-refractory-myasthenia-gravis/download>	1-3, 7-10, 18, 21, 26 ---------- 4-6, 22-25, 27
Y	(STEGALL, M) Dosing Regimen of Eculizumab Added to Conventional Treatment in Positive Cross Match Living Donor Kidney Transplant. Clinical Trials. 08 June, 2015 [retrieved on 02 October, 2017]; pages 1-6; page 3/6, lines 16-17; retrieved from the internet <https://clinicaltrials.gov/ct2/show/NCT00670774>	4-6
Y	(EUROPEAN MEDICINES AGENCY) Scientific Discussion- Soliris, Inn: Eculizumab. 2007 [retrieved on 02 October, 2017]; pages 1-41; page 8/41, paragraph 3; retrieved from the internet <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000791/WC500054212.pdf >.	22
Y	US 2015/0299305 A1 (ALEXION PHARMACEUTICALS, INC.) 22 October, 2015; paragraphs [0068]-[0069]; claims 5-6	23-24

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 October 2017 (03.10.2017)	19 OCT 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/32767

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/32767

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-Please See Supplemental Page-*-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Groups I+, Claims 1-30; SEQ ID NO: 10 (heavy chain)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/32767

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	(HOWARD, JF et al.) A Randomized, Double-Blind, Placebo-Controlled Phase II Study of Eculizumab in Patients with Refractory Generalized Myasthenia Gravis. Muscle and Nerve. 30 April, 2013; Vol. 48, No. 1; pages 76-84; page 77, column 1, paragraph 1; page 77, column 2, paragraph 3; page 78, column 1, paragraphs 2-3; page 83, column 1, paragraph 1	25
Y	(GATAULT, P et al.) Therapeutic Drug Monitoring of Eculizumab: Rationale for an Individualized Dosing Schedule. 04 September, 2015; Vol. 7, No. 6; pages 1205-1211; abstract; page 1207, column 2, paragraph 2; DOI: 10.1080/19420862.2015.1086049	27
A	(TAPIA, CB) Development and Validation of a New Measure of Impairment in Myasthenia Gravis: The Myasthenia Gravis Impairment Index [online]. University of Toronto. 2015; downloaded from the internet < https://tspace.library.utoronto.ca/bitstream/1807/70877/1/Barnett_Tapia_Carolina_201511_PhD_thesis.pdf>; page 34, paragraph 2	11-14, 19-20
A	(LAI, JS et al.) Quality-of-Life Measures in Children with Neurological Conditions: Pediatric Neuro-QOL. Neurorehabilitation, and Neural Repair. 25 July, 2011; Vol. 26, No. 1; pages 1-19; page 8, paragraph 1; DOI: 10.1177/1545968311412054	15-16
A	(WINTER, Y et al.) Health-Related Quality of Life in ALS, Myasthenia Gravis and Facioscapulohumeral Muscular Dystrophy. Journal of Neurology. 10 April, 2010; Vol. 257, No. 9; pages 1473-1481; abstract; page 1476, column 2, paragraph 2; DOI: 10.1007/s00415-010-5549-9	17
A	(SANDERS, DB et al.) Immunosuppressive Therapies in Myasthenia Gravis. Autoimmunity. August, 2010; Vol. 43, No. 5-6; pages 428-435; page 431, column 2, paragraph 2; DOI: 10.3109/08916930903518107	28-30

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US17/32767

-***-Continued from Box No. III: Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-30; and SEQ ID NO: 10 are directed toward a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering a therapeutically effective amount of eculizumab to the patient.

The method will be searched to the extent that it comprises eculizumab encompassing SEQ ID NO: 10 (first exemplary heavy chain). Applicant is invited to elect additional heavy chain sequence(s), with specified SEQ ID NO: for each to be searched. Additional heavy chain sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1-23, 24 (in-part), and 25-30 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 10 (heavy chain). Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be an eculizumab variant encompassing SEQ ID NO: 14 (first exemplary elected heavy chain).

No technical features are shared between the antibody sequences of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering a therapeutically effective amount of eculizumab to the patient; wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability; and wherein the patient is administered eculizumab for at least 26 weeks; a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient; wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability; wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses ofeculizumab on days 7, 14, and 21, and administering 1200 mg of eculizumab as a fifth induction dose on day 28; wherein the patient is administered eculizumab for at least 26 weeks; wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter; and wherein the patient has a clinically meaningful improvement (reduction) in at least two measurements of generalized myasthenia gravis severity selected from the group consisting of MG-ADL, QMG, MGC, MG-QOL, and Neuro-QOL; a method of treating refractory generalized myasthenia gravis in a patient in need thereof comprising administering eculizumab to the patient; wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability; wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg of eculizumab as a fifth induction dose on day 28; wherein the patient is administered eculizumab for at least 26 weeks; wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter; and wherein the patient has a clinically meaningful improvement (reduction) in five measurements of generalized myasthenia gravis severity, wherein the five measurements of generalized myasthenia gravis severity are a reduction in MG-ADL of at least 3 points, a reduction of QMG of at least 4 points, a reduction in MGC of at least 6 points, a reduction in MG-QOL of at least 6 points, and a reduction in Neuro-QOL of at least 8 points.

However, these shared technical features are previously shared by the publication entitled 'A Randomized, Double-Blind, Placebo-Controlled Phase II Study of Eculizumab in Patients with Refractory Generalized Myasthenia Gravis' to Howard, et al. (hereinafter 'Howard') in view of the publication entitled 'Safety and Efficacy of Eculizumab in Refractory Generalized Myasthenia Gravis (REGAIN Study)' (ClinicalTrials) in further view of the publication entitled 'Development and Validation of a New Measure of Impairment in Myasthenia Gravis: the Myasthenia Gravis Impairment Index' (Tapia).

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from Previous Supplemental Box-***-

Howard discloses a method of treating refractory generalized myasthenia gravis in a patient in need thereof (a method of treating refractory generalized myasthenia gravis in a patient in need thereof; page 1, second paragraph) comprising administering a therapeutically effective amount of eculizumab to the patient (comprising administering a therapeutically effective amount of eculizumab to the patient; page 1, second-third paragraphs; page 1 – page 2, first – third paragraphs); wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) (wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR); page 2, fifth paragraph) and shows marked generalized weakness or bulbar signs and symptoms of myasthenia gravis while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability (requires chronic plasma exchange or chronic IVIg to maintain clinical stability; page 2, eighth paragraph); A method of treating refractory generalized myasthenia gravis in a patient in need thereof (a method of treating refractory generalized myasthenia gravis in a patient in need thereof; abstract) comprising administering a therapeutically effective amount of eculizumab to the patient (comprising administering a therapeutically effective amount of eculizumab to the patient; abstract; page 79, first column, second paragraph); wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) (wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR); page 79, first column, third paragraph) and shows marked generalized weakness while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) (shows marked generalized weakness while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST); page 79, first column, third paragraph) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability (requires chronic plasma exchange or chronic IVIg to maintain clinical stability; page 80, second column, second paragraph; page 84, first column, third paragraph); and wherein the patient is administered eculizumab for at least 26 weeks (figure 1); a method of treating refractory generalized myasthenia gravis in a patient in need thereof (a method of treating refractory generalized myasthenia gravis in a patient in need thereof; abstract) comprising administering eculizumab to the patient (comprising administering a therapeutically effective amount of eculizumab to the patient; abstract; page 79, first column, second paragraph); wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) (wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR); page 79, first column, third paragraph) and shows marked generalized weakness while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) (shows marked generalized weakness while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST); page 79, first column, third paragraph) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability (requires chronic plasma exchange or chronic IVIg to maintain clinical stability; page 80, second column, second paragraph; page 84, first column, third paragraph); wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering an induction dose of eculizumab on day 1 (wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering an induction dose of eculizumab on day 1; figure 1; page 79, first column, second paragraph), administering 900 mg doses of eculizumab (page 79, first column, second paragraph), and administering a fifth induction dose (page 79, first column, second paragraph); wherein the patient is administered eculizumab for at least 26 weeks (figure 1); wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter (wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering eculizumab 14 days after the fifth induction dose and administering eculizumab every 14 ± 2 days thereafter; page 79, first column, second paragraph); and wherein the patient has a clinically meaningful improvement (reduction) in at least two measurements of generalized myasthenia gravis severity selected from the group consisting of MG-ADL (page 82, second column, second paragraph), and QMG (figure 4); a method of treating refractory generalized myasthenia gravis in a patient in need thereof (a method of treating refractory generalized myasthenia gravis in a patient in need thereof; abstract) comprising administering eculizumab to the patient (comprising administering a therapeutically effective amount of eculizumab to the patient; abstract; page 79, first column, second paragraph); wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR) (wherein the patient is positive for auto-antibodies binding to nicotinic acetylcholine receptor (anti-AChR); page 79, first column, third paragraph) and shows marked generalized weakness while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST) (shows marked generalized weakness while receiving therapy for myasthenia gravis including anticholinesterase inhibitor therapy and immunosuppressant therapy (IST); page 79, first column, third paragraph) and requires chronic plasma exchange or chronic IVIg to maintain clinical stability (requires chronic plasma exchange or chronic IVIg to maintain clinical stability; page 80, second column, second paragraph; page 84, first column, third paragraph); wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1 (wherein eculizumab is administered using a phased dosing schedule with an induction phase comprising administering an induction dose of eculizumab on day 1; figure 1; page 79, first column, second paragraph), administering 900 mg doses of eculizumab (page 79, first column, second paragraph), and administering a fifth induction dose (page 79, first column, second paragraph); wherein the patient is administered eculizumab for at least 26 weeks (figure 1); wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter (wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering eculizumab 14 days after the fifth induction dose and administering eculizumab every 14 ± 2 days thereafter; page 79, first column, second paragraph); and wherein the patient has a clinically meaningful improvement (reduction) measurements of generalized myasthenia gravis severity (page 82, second column, second paragraph; figure 4; table 3), wherein the five measurements of generalized myasthenia gravis severity are a reduction in MG-ADL of at least 3 points (page 82, second column, second paragraph; table 3), a reduction of QMG of at least 4 points (figure 4). Howard further discloses MG-QOL (page 78, second column, third paragraph).

Howard does not disclose a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses ofeculizumab on days 7, 14, and 21, and administering 1200 mg ofeculizumab as a fifth induction dose on day 28; wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter; a reduction in MGC of at least 6 points, a reduction in MG-QOL of at least 6 points, and a reduction in Neuro-QOL of at least 8 points.

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from Previous Supplemental Box-***-

ClinicalTrials discloses a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1 (page 1), administering 900 mg doses of eculizumab on days 7, 14, and 21 (administering 900 mg of eculizumab weekly X4; page 1), and administering 1200 mg of eculizumab as a fifth induction dose on day 28 (and administering 1200 mg of eculizumab as a fifth induction dose week 5 (on day 28); page 2); wherein the patient is administered eculizumab for at least 26 weeks (page 1); wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter (wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab every 2 weeks (14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter); page 2).

Tapia discloses MGC (page 37, fourth paragraph – page 38; pages 238-239) and Neuro-QOL (page 210) for outcome measurement (page 37, fourth paragraph – page 38; page 210;pages 238-239).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the disclosure of Howard, to include a phased dosing schedule with an induction phase comprising administering a 900 mg induction dose of eculizumab on day 1, administering 900 mg doses of eculizumab on days 7, 14, and 21, and administering 1200 mg ofeculizumab as a fifth induction dose on day 28; wherein the 28 day induction phase of eculizumab treatment is followed by a maintenance phase comprising administering 1200 mg of eculizumab 14 days after the fifth induction dose and administering 1200 mg of eculizumab every 14 ± 2 days thereafter, as previously disclosed by ClinicalTrials, in order to provide a superior dosing schedule for the administration of eculizumab to effectively treat myasthenia gravis. Furthermore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the disclosure of Howard, to incorporate MGC and Neuro-QOL for outcome measurement, as disclosed by Tapia, for providing a superior method to assess the efficacy of eculizumab in treating refractory generalized myasthenia gravis in a patient. Additionally, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the disclosure of Howard, regarding an appropriate level of improvement with effective treatment, wherein the appropriate level of improvement would have been measurable using known indices for the assessment of subjects with MG, including a reduction in MGC of at least 6 points, a reduction in MG-QOL of at least 6 points, and a reduction in Neuro-QOL of at least 8 points would have been obvious to a person of ordinary skill in the art at the time the invention was made.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Howard, ClinicalTrials and Tapia refernces, unity of invention is lacking.