1 August 2017
EMA/410939/2017
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Soliris

International non-proprietary name: eculizumab

Procedure No. EMEA/H/C/000791/II/0090

Marketing authorisation holder (MAH): Alexion Europe SAS

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Alexion Europe SAS submitted to the European Medicines Agency on 5 December 2016 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication of Soliris to include the treatment of refractory generalised myasthenia gravis (gMG) patients who are anti-acetylcholine receptor (AChR) antibody-positive; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Summary of Product Characteristics (SmPC) are updated to include information on the new indication and to include the new methodology to calculate the Adverse Drug Reaction frequencies (section 4.8). The Package Leaflet and the Risk Management Plan (RMP [version 14.0]) are updated accordingly.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet and to the RMP.

Soliris, was designated as an orphan medicinal product EU/3/09/653 on 24 July 2009. Soliris was designated as an orphan medicinal product in the following indication: Treatment of atypical haemolytic uremic syndrome (aHUS).

Soliris, was designated as an orphan medicinal product EU/3/03/166 on 17 October 2003. Soliris was designated as an orphan medicinal product in the following indication: Treatment of paroxysmal nocturnal haemoglobinuria (PNH).

The new indication, which is the subject of this application, falls within a separate orphan designation EU/3/14/1304 granted on 29 July 2014.

After the adoption of the opinion for this variation in June 2017, the wording in SmPC section 4.1 was revised to clarify the target population as adults only. All other aspects of the application remained unchanged. A revised opinion was adopted in August 2017.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0185/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0185/2016 was not yet completed as some measures were deferred.

In addition, the PIP P/0290/2014 for PNH and aHUS indication was previously completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The marketing authorisation holders (MAH) received Protocol Assistance at the Committee for Medicinal Products for Human Use (CHMP) on 30 May 2013. The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: N/A

Timetable	**Actual dates**
Submission date	5 December 2016
Start of procedure:	24 December 2016
CHMP Rapporteur Assessment Report	28 February 2017
PRAC Rapporteur Assessment Report	24 February 2017
PRAC members comments	1 March 2017
Updated PRAC Rapporteur Assessment Report	2 March 2017
PRAC Outcome	9 March 2017
CHMP members comments	13 March 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 March 2017
Request for supplementary information	23 March 2017
MAH's responses submitted to the CHMP on:	21 April 2017
CHMP Rapporteur Assessment Report	5 June 2017
PRAC Rapporteur Assessment Report	26 May 2017
PRAC members comments	31 May 2017
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	9 June 2017
CHMP members comments	12 June 2017
Updated CHMP Rapporteur Assessment Report	16 June 2017
Opinion	22 June 2017
Start of written procedure	31 July 2017

CHMP members comments	1 August 2017
Opinion	1 August 2017

2. Scientific discussion

2.1. Introduction

Eculizumab is a humanized recombinant monoclonal antibody that binds to the human complement component 5 (C5) complement protein and inhibits C5 cleavage to C5a and C5b, preventing the generation of the terminal complement complex C5b-9 and thus blocking complement-mediated cell lysis and activation.

The antibody is an immunoglobulin g (IgG)2/4 kappa immunoglobulin comprised of human constant regions and murine complementarity-determining regions (CDRs) grafted onto human framework light- and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

Currently, Soliris (eculizumab) is approved for Paroxysmal Nocturnal Hemoglobinuria (PNH) and atypical Haemolytic Uremic Syndrome (aHUS).

This was an application for an Extension of Indication of Soliris to include the 'treatment of Refractory generalised myasthenia gravis (gMG) patients who are antiacetylcholine receptor (AChR) antibody-positive'.

Myasthenia gravis (MG) is an autoimmune disease in which antibodies bind to acetylcholine receptors or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction (NMJ). The antibodies induce fluctuant weakness of skeletal muscles. In about two-thirds of patients, the first symptom is weakness of extrinsic ocular muscles. In 1 of 10 MG patients, symptoms remain limited to extrinsic ocular muscles (ocular myasthenia gravis). However, in the majority of patients, the symptoms progress and proceed to affect other bulbar muscles as well as limb muscles (generalised MG)[1,2].

Myasthenia gravis is considered to affect less than 2 in 10,000 people in the European Union (EU)[3].

The diagnosis of myasthenia gravis is confirmed by the combination of relevant symptoms and signs and a positive test for specific autoantibodies (antibodies against acetylcholine receptors, muscle-specific kinase, and lipoprotein receptor– related protein)[4].

Current treatment options include acetylcholinesterase inhibitors, short-term immune therapies such as plasmapheresis or intravenous immunoglobulin (IVIG), and long-term immune therapies with immunosuppressive agents such as corticosteroids, azathioprine (AZA), and cyclosporine (CYC). Thymectomy is also a treatment option[5]. There is a distinct subset of patients, however, who continue to experience significant symptoms and morbidities despite best available treatment with existing MG therapies. These patients are often referred to as having treatment-refractory myasthenia. The exact prevalence of refractory myasthenia is unknown, but it is estimated to occur in approximately 10% of patients with gMG[6].

[1] Gilhus NE. Myasthenia Gravis. N Engl J Med 2016;375:2570-81.
[2] Ivicic T. Myasthenia gravis: a review. : http://dx.doi.org/10.17486/gyr.3.1036
[3] EMA/COMP/374393/2014 Rev.1
[4] Barnett C, Bril V, Kapral M, Kulkarni A, Davis AM (2014) A Conceptual Framework for Evaluating Impairments in Myasthenia Gravis. PLoS ONE 9(5): e98089.
[5] Suh J, Goldstein J, Nowak RJ. Clinical Characteristics of Refractory Myasthenia Gravis. Yale Journal of Biology and Medicine 2013 (86):255-260.
[6] Silvestri NJ, Wolfe GI. Treatment-Refractory Myasthenia Gravis. J Clin Neuromusc Dis 2014;15:167–178

Information on Paediatric requirements

A Paediatric Investigation Plan (PIP) has been agreed with the Paediatric Committee (PDCO) for eculizumab in the treatment of Myasthenia Gravis.

The initial EMA decision is dated 26 February 2016 (EMEA-000876-PIP05-15). A subsequent request for modification of the agreed PIP has been submitted on 07 March 2016 and the latest version of the PIP decision is dated 15 July 2016 (EMEA-000876-PIP05-15-M01).

Treatment of myasthenia gravis

The waiver applies to:

• the paediatric population from birth to less than 6 years of age;

• for concentrate for solution for infusion, intravenous use;

• on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset(s).

2.2. Non-clinical aspects

A full nonclinical package was included in the original Marketing Authorisation Application (MAA) for Soliris presented in 2007. With the exception of the published studies discussed in the below assessment, no additional nonclinical data have been generated.

Direct testing of eculizumab in nonclinical models of MG is precluded by eculizumab being a highly specific monoclonal antibody that binds only to human C5. Eculizumab has not been shown to bind to C5 from any other mammalian species tested. In the initial MAA, only in vitro pharmacodynamic studies were performed as eculizumab has minimal cross-reactivity with non-primate and primate species.

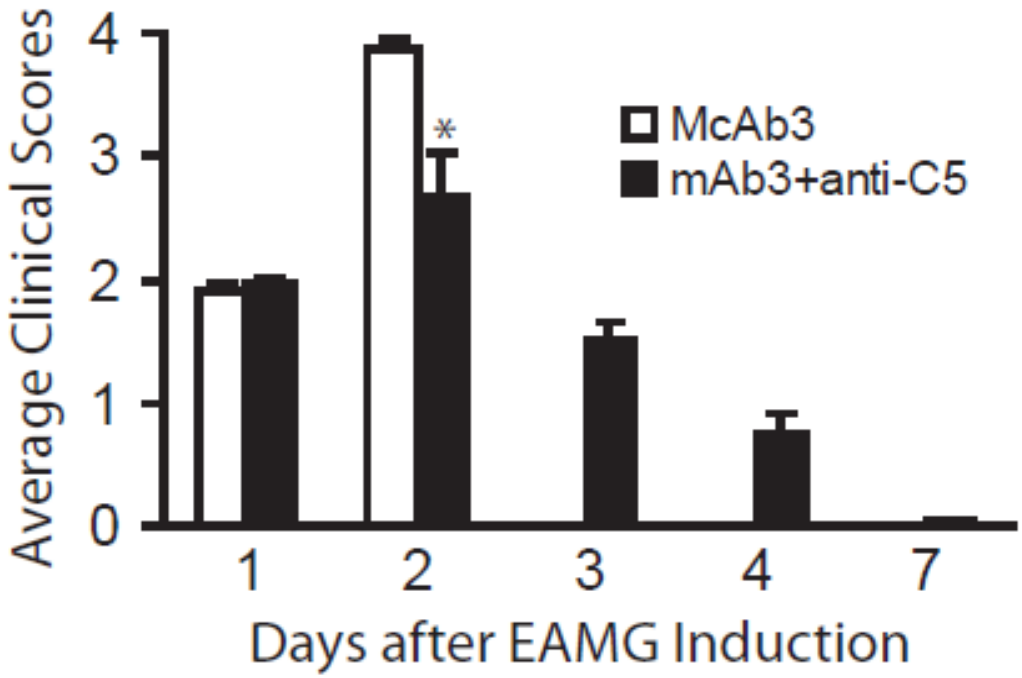
A study was published (Zhou 2007) using a rodent model of C5 inhibition in experimental acquired MG which constituted the rationale for evaluating eculizumab in patients with MG.

2.2.1. Pharmacology

The effect of pre-treatment of anti-C5 mAb to block experimentally acquired myasthenia gravis (EAMG) in Lewis rats was evaluated (Zhou 2007). Intraperitoneal injections of rat anti-mouse muscle AchR monoclonal IgG2b isotype antibody (McAb3) to rats resulted in EAMG. Within 24 hours of administration, the animals developed hunched posture and dragged their legs while walking (strength score grade 3 weakness) and within 48 hours became moribund (strength score grade 4 weakness). In contrast, rats pre-treated with the anti-C5 mAb did not show evidence of muscle weakness (strength score grade 0 weakness) after McAb3 administration.

In another experiment, EAMG was induced in rats on Day 0 and 24 hours later, animals were administered anti-C5 mAb. At the 48 hours from EAMG induction, anti-C5 mAb treated rats showed strength scores improvement compared to the control animals (see Figure 1). By 72 hours from EAMG induction, anti-C5 mAb treated rats further improved and were normal by Day 7 (strength score grade 0 weakness), while the control rats developed more severe EAMG and required euthanasia.

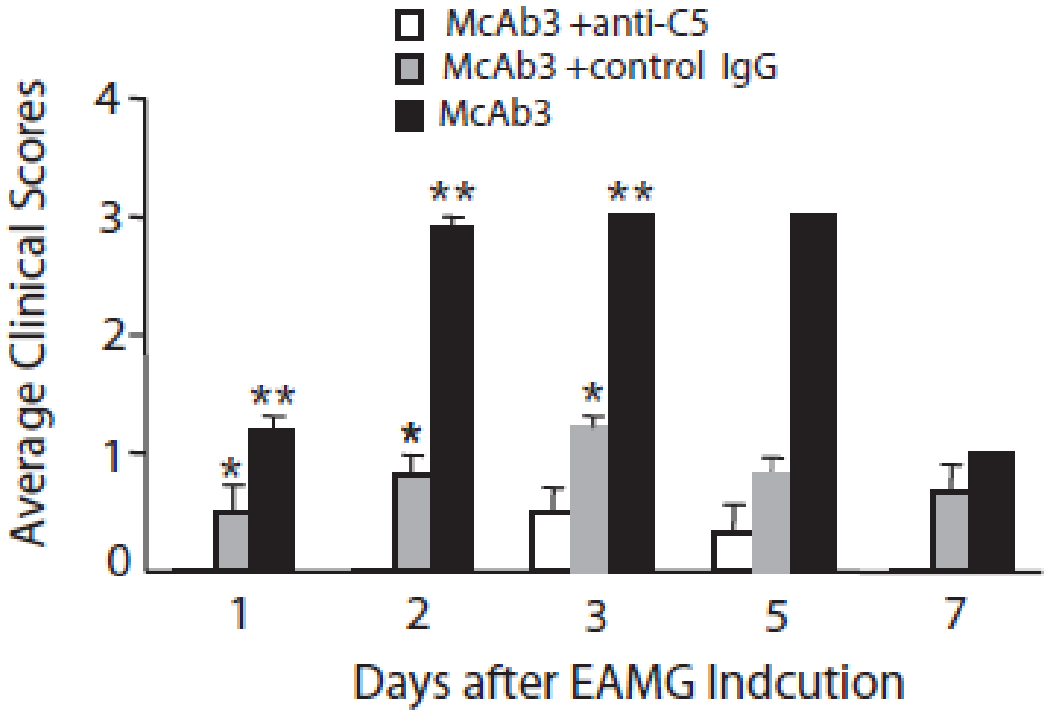
Figure 1 Clinical Scores of Rats Treated with or without Anti-C5 mAb 24 hours After Experimentally Acquired Myasthenia Gravis Induction (Zhou, 2007).



On day 0, 11 rats were administered McAb-3 to induce EAMG. On day 1, these rats developed symptoms of EAMG and the clinical scores are around 2. Six of these rats were randomly chosen and treated with anti-C5 mAb. Although rats treated with anti-C5 mAb became slightly worse on day 2 compared with day 1, they had significantly better disease severity scores compared with untreated rats (*, $p<0.014$) and the untreated rats developed such severe weakness that they underwent euthanasia. The anti-C5 mAb-treated rats that were not sacrificed for tissue collection gradually recovered. Results are shown as means ± SE.
Abbreviations: AChR = acetylcholine receptor; C5 = complement component 5; EAMG = experimentally acquired myasthenia gravis; h= hours; mAb = monoclonal antibody; McAb = muscle AChR monoclonal IgG2b isotype antibody; SE = standard error

A third set of experiments were designed to evaluate whether the therapeutic effect of anti-C5 mAb treatment was specific to complement inhibition. Rats were treated with 1) non-neutralizing anti-C5 mAb, 2) neutralizing anti-C5 mAb, or 3) no mAb. Four hours later all groups were administered McAb3. The control rats (no mAb) and the rats treated with non-neutralizing anti-C5 mAb showed weakness at 24 hours that became progressively worse by Day 7, whereas rats treated with neutralizing anti-C5 mAb were normal at 24 hours and throughout to Day 7 (Figure 2). Single injection of the neutralizing anti-C5 mAb depleted serum C5 activity at 48 and 72 hours after administration. By Day 7 serum C5 activity had returned to normal. No alteration of C5 activity occurred upon injection of non-neutralizing anti-C5 mAb.

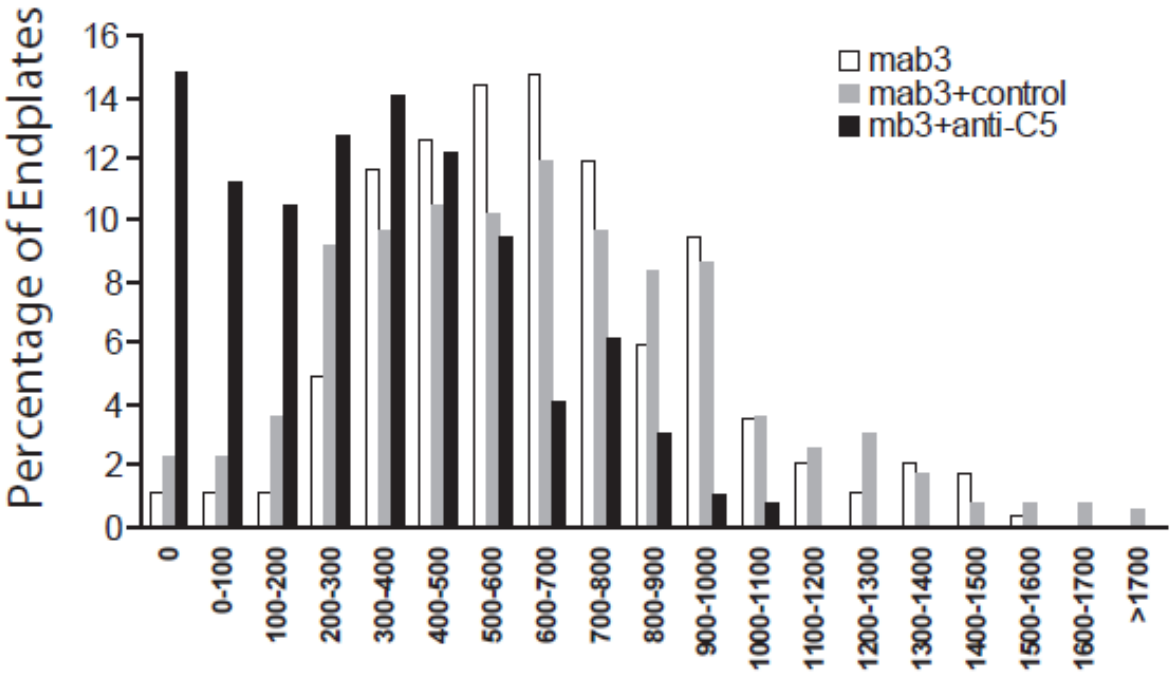
Figure 2 Clinical Scores of EAMG Rats Treated with Anti-C5 mAb or Control IgG (Zhou, 2007).



Rats received anti-C5 mAb or control IgG 4 h before EAMG induction. Rats receiving McAb-3 alone (n = 5) developed EAMG on day 1, which became severe at day 2. In comparison, rats pretreated with anti-C5 mAb (n = 6) had clinical scores of 0 (**, $p<0.0001$) at both days 1 and 2, whereas rats pretreated with control IgG Ab (n = 6) developed weakness of intermediate severity, which is significantly higher than anti- C5 mAb-treated rats ($p<0.05$). On day 3, two of the six rats pretreated with anti-C5 mAb developed mild EAMG and recovered by day 5. Results are shown as means ±SE.
Abbreviations: AChR = acetylcholine receptor; C5 = complement component 5; EAMG = experimentally acquired myasthenia gravis; IgG = immunoglobulin G; mAb = monoclonal antibody; McAb = muscle AChR monoclonal IgG2b isotype antibody; SE = standard error

Complement component 9 (C9) is a member of the complement membrane attack complex (MAC), whereas complement component 3 (C3) plays a central role in the activation of the alternative pathway of the complement system. Assembly of the MAC at the NMJ plays an essential role in the destruction of the post-synaptic structure, compromising neuromuscular transmission in the EAMG model. Immunofluorescence staining of NMJs of EAMG muscles showed that treatment with the neutralizing anti-C5 mAb reduced C9 deposition (Figure 3) whereas treatment with non-neutralizing control mAb did not. Muscles from the untreated and non-neutralizing anti-C5 mAb-treated rats contained a higher percentage of NMJs with high density C0 deposits than muscles from IgG-neutralizing anti-C5 mAb-treated rats. No changes were noted for C3 immunoreactivity at NMJs consistent with the inhibition of the complement cascade at a step subsequent to activation of C3.

Figure 3 Anti-C5 mAb Treatment Reduced the Intensity of C9 Immunofluorescence at the Neuromuscular Junction (Zhou, 2007).

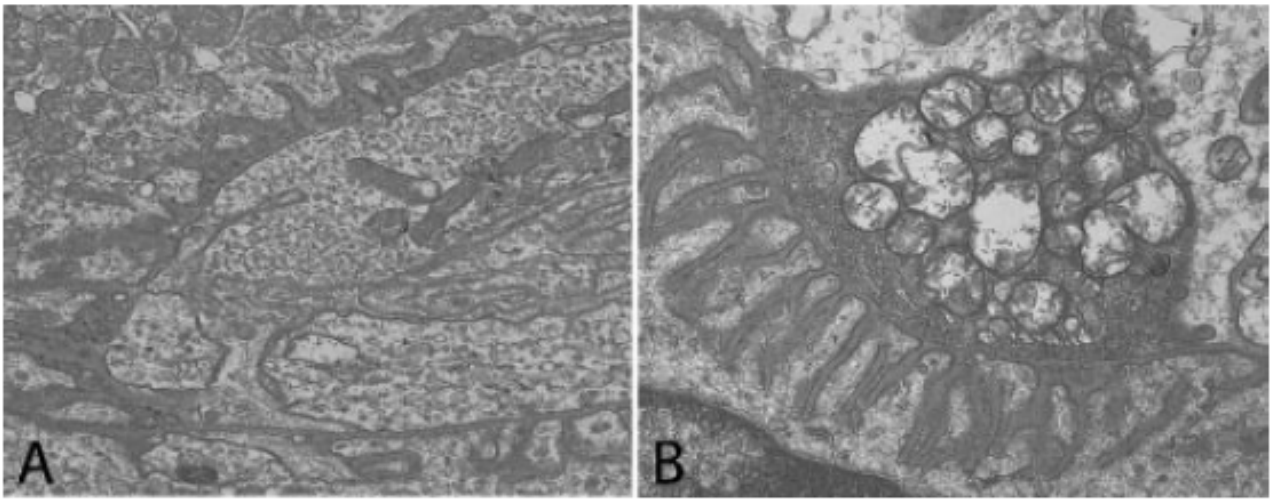


This graph shows the percentage of neuromuscular junctions within certain fluorescence intensity range from EAMG rats, EAMG rats treated with anti-C5 mAb, and EAMG rats treated with control IgG. The intensities of junctions from anti-C5 mAb-treated rats were shifted to the lower intensity ranges and is significantly weaker than the other two groups ($p<0.0001$ for the nonparametric Kolmogorov-Smirnov two-sample test). There is no significant difference in the distribution of fluorescence intensity between the junctions of untreated and control IgG-treated rats.
Abbreviations: C5 = complement component 5; C9 = complement component 9; EAMG = experimentally acquired myasthenia gravis; IgG = immunoglobulin G; mAb = monoclonal antibody

Ultrastructural analysis of NMJs from diaphragms of the control rats showed severe EAMG features such as simplification of junctional folds, widened synaptic clefts and electron-dense material consistent with sloughed synaptic membrane (Figure 4A). In contrast, the NMJs from diaphragms of neutralizing anti-C5 mAb treated rats showed negligible changes (Figure 4B). In addition, diaphragm sections from neutralizing anti-C5 mAb-treated rats showed significantly lower numbers of inflammatory cells such as monocytes and macrophages, that are typical features of passively induced EAMG, compared with sections from untreated and IgG control non-neutralizing anti-C5 mAb-treated rats.

Figure 4 Anti-C5 mAb Treatment Preserves the Integrity of the Neuromuscular Junctions (Zhou,

2007).



Electrical microscopy was performed to study the structure of neuromuscular junctions of diaphragms of EAMG rats. The neuromuscular junctions from untreated EAMG rats (A) were abnormal. They either had shortened or no junctional folds, widened junctional space, widened synaptic cleft, or electron-dense spots that contained AChR-rich membrane. The neuromuscular junctions from anti-C5 mAb-treated rats (B), in contrast, had relatively normal junctional folds and space and normal synaptic cleft with some membrane blebbing.
Abbreviations: AChR = acetylcholine receptor; C5 = complement component 5; EAMG = experimentally acquired myasthenia gravis; mAb = monoclonal antibody

2.2.2. Ecotoxicity / environmental risk assessment

Due to the fact that eculizumab is a protein and according to the requirements set in the CHMP guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, no Environmental Risk Assessment for SOLIRIS was provided for this type II variation, and this was considered acceptable.

2.2.3. Discussion on non-clinical aspects

The study data provided by the Applicant shows that inhibition of complement with a blocking anti-C5 mAb is able to protect from development of severe EAMG in rats. Complement component 5 blockade prevented weakness in EAMG and depletion 24 hours after disease initiation stopped disease progression. In addition, histological studies showed that NMJ architecture was maintained and C9 deposition at NMJs (related to the destruction of the post-synaptic structure and compromised neuromuscular transmission in the EAMG model) was significantly reduced.

2.2.4. Conclusion on the non-clinical aspects

A full nonclinical package was included in the original MAA for Soliris presented in 2007. With the exception of the published studies discussed in this report, no additional nonclinical data have been generated. This was considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

Good Clinical Practice

The Clinical trials were performed in accordance with Good Clinical Practice (GCP) as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1 Eculizumab trials in Refractory Myasthenia Gravis

Descriptor	Study Number		
	ECU-MG-301	ECU-MG-302	C08-001
Phase	3	3	2
Study Design	Multicenter, multinational, double-blind, placebo-controlled, randomized, parallel group; Efficacy, Safety, and PK/PD	Multicenter, multinational, open-label extension; Efficacy, Safety, and PK/PD	Multicenter, double-blind, placebo-controlled, randomized, crossover; Efficacy, Safety, and PK/PD
Countries[a]	Argentina, Belgium, Brazil, Canada, CZ, Denmark, Finland, Hungary, Italy, Korea, Netherlands, Spain, Sweden, Turkey, UK, Japan, US	Argentina, Belgium, Brazil, Canada, CZ, Denmark, Finland, Hungary, Italy, Korea, Netherlands, Spain, Sweden, Turkey, UK, Japan, US	US, UK
Study Status	Completed	Ongoing	Completed
Number of Patients Randomized	126	NA	14
Number of Patients Treated	125 (62 eculizumab, 63 placebo)	114 eculizumab[b]	14 (13 eculizumab, 13 placebo)
Number of Patients Completed	118	Ongoing, 7 patients discontinued as of 01 Mar 2016 cutoff	11
Included in Clinical Pharmacology Analysis	Yes	No	Yes
Dosing Regimen	Induction: 900 mg every week Maintenance:1200 mg every 2 weeks	Induction (placebo pts[c]): 900 mg every week Maintenance (all pts): 1200 mg every 2 weeks	Induction: 600 mg every week Maintenance: 900 mg every 2 weeks
Analysis cutoff date for CSR	19 Feb 2016[d]	01 Mar 2016	16 Mar 2011[d]

(a) Includes countries that enrolled patients; (b) 117 patients enrolled to date, 114 as of the data cut-off, and 113 included in the interim analysis (1 patient from Sweden was excluded, because the Sweden Health Authority did not approve the protocol amendment that allowed for the interim analysis), 98 with efficacy data included in the analysis; (c) This dosing regimen (900 mg every week) is for those patients who received placebo in Study ECU-MG-301 (d) Date last patient completed

Abbreviations: CSR = clinical study report; CZ = Czech Republic; PD = pharmacodynamic(s); PK =pharmacokinetic(s); pts = patients; UK = United Kingdom; US = United States

2.3.2. Pharmacokinetics

Data from 2 studies were included in the current population pharmacokinetics (Pop-PK) and PK/pharmacodynamics (PD) analyses, Study C08-001 and Study ECU-MG-301 (Table 1). Analyses of PK/PD data from Study ECU-MG-302 were not available at the time of this assessment.

The total eculizumab concentration (bound plus free) in human serum was measured using an enzyme-linked immuno-sorbent assay (ELISA) utilizing human C5 as the capture reagent and (horseradish peroxidase) HRP-anti-human IgG4 for detection.

Due to the method IM-1727-112 being validated more than 1 year after BTM-0056 was last used for clinical sample analysis, it was not possible to undertake a formal cross-validation. Reagents and reference standards previously used to analyse clinical study samples with method SOPLUS-BTM-0056 were no longer within stability limits. Comparisons at the time of method transfer from Alexion to MPI, using new materials, showed the assay methods produce numerically similar results for measurement of eculizumab in human serum. As described in the white paper ECU-MG PK Variability Assessment the majority (≈70%) of these differences in exposure is attributed to differences in assays used in Studies C08-001 and ECU-MG-301, represented by an assay conversion factor with a power term of 1.07 (95% CI: 1.05, 1.09). The remaining approximately 30% residual variability that cannot be explained by the assay conversion factor is likely due to random variance associated with the 2 studies having different sample sizes. Random variances include such things as inter- and intra-subject variabilities in eculizumab PK. In addition, the results of these comparisons showed reproducibility between the methods, with percent difference (%D) values within ± 30% for at least two-thirds of the samples evaluated, which is in accordance with incurred sample reanalysis (ISR) acceptance criteria in the applicable guidance from EMA (Bioanalytical Method Validation, EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2, adopted 21 Jul 2011, effective 01 Feb 2012). However, comparability of the assay methods cannot be concluded, as these method comparison studies were not conducted in accordance with all aspects of the regulatory guidance.

The pre-study validation or method development of all these bioanalytical methods was consistent with the state-of-the-art. These validations demonstrated an adequate precision and accuracy (both intra- and inter-day) within the calibrated range, which showed an adequate selectivity and sensitivity. No formal cross-validation has been performed. This is not a major problem when studies are assessed individually since all the analytical methods employed were validated. This could be a problem if different methods had been used within a study. In the case of Pop-PK analyses performed with data from several studies, the validity of the pooling can be assumed if a factor for the study is non-significant.

Measurement of chicken red blood cell (cRBC) haemolytic activity was performed using validated qualitative methods. Different cRBC haemolytic assays based upon a common methodology were used for samples from Studies C08-001 (VP-QCP-0041-FR, 2000) and ECU-MG-301 (1727-097, 2015). A cross-validation between both methods was performed. Samples prepared from a source outside of MPI Research were supplied for testing. Controls can be used immediately upon thawing. Sponsor supplied controls all performed within acceptance criteria. The results indicate relative haemolysis is consistent across test sites.

Free C5 was quantified using a validated ELISA. Standards and quality control (QC) samples for each study met the respective assay acceptance criteria established in method validation.

Study samples determined to be positive for anti-drug antibodies (ADA) were also analysed for neutralizing activity towards eculizumab. The principle of the neutralizing antibody assay was competition of C5 binding to eculizumab. In brief, biotin-conjugated eculizumab was coated on an assay plate. Successively with washing, test samples and then MSD Sulfo-Tag conjugated C5 (C5-STAG) were added to the analytical plate. The presence of neutralizing ADA (NAb) in a test sample competitively blocks C5-STAG binding to eculizumab and results in a decrease in signal.

The in-study validation shows an acceptable calibration standards and QC values for both sudies. In general, the analysis of study samples is acceptable and the re-analysis of the study samples was well justified and handled, although according to the Applicant study samples were analysed outside of established long term stability for pharmacokinetic, free C5, and haemolytic analysis. Stability testing is ongoing under the respective validation studies to cover sample storage. In the opinion of the Bioanalytical Monitor, this event may impact the quality and integrity of the study if stability is not established. The Applicant is requested to submit the stability data when available (See Section 4).

No ISR was performed for Study C08-001. For Study ECU-MG-301, total pass rate was 67.6%, 145 total run with 98 acceptable results. For Study ECU-MG-302 has had 25 of 320 total PK samples tested for reproducibility thus far, with 21 (84%) having a percent difference less than 30%, meeting the acceptance criteria for ISR.

2.3.3. Pharmacodynamics

Mechanism of action

Eculizumab is a humanized monoclonal antibody that specifically binds with high affinity to the human terminal C5, inhibiting C5 enzymatic cleavage and thereby preventing the generation of the proinflammatory/prothrombotic complement activation products C5a and the cytolytic and proinflammatory/prothrombotic MAC C5b-9 that are responsible for the inflammatory consequences of terminal complement activation. Given that terminal complement-mediated cell damage and inflammation at the NMJ play a central role in the pathophysiology of autoimmune-mediated MG (Tüzün 2013), the mechanism of action of eculizumab as a potent and selective terminal complement inhibitor supports its use in the management of refractory gMG mediated by complement-activating antibodies directed against the NMJ.

The use of eculizumab (Anti-C5 mAb) in this condition is based on the role of the complement activation at the NMJ in MG as one of the effectors mechanisms. Antibodies directed against the acetylcholine receptor (AChR) have been identified that bind complement and initiate the complement cascade producing a complement-mediated lysis of the NMJ via formation of MACs[7,8,9]. Eculizumab blocks the formation of terminal complement complex by selectively preventing the enzymatic cleavage of C5. Antibodies can also cause an impairment of the NMJ by direct blockade of ACh binding sites inhibiting the opening of the ion channel or cross-linking of AChRs by divalent Abs accelerating endocytosis and degradation of AChRs.

Primary and secondary pharmacology

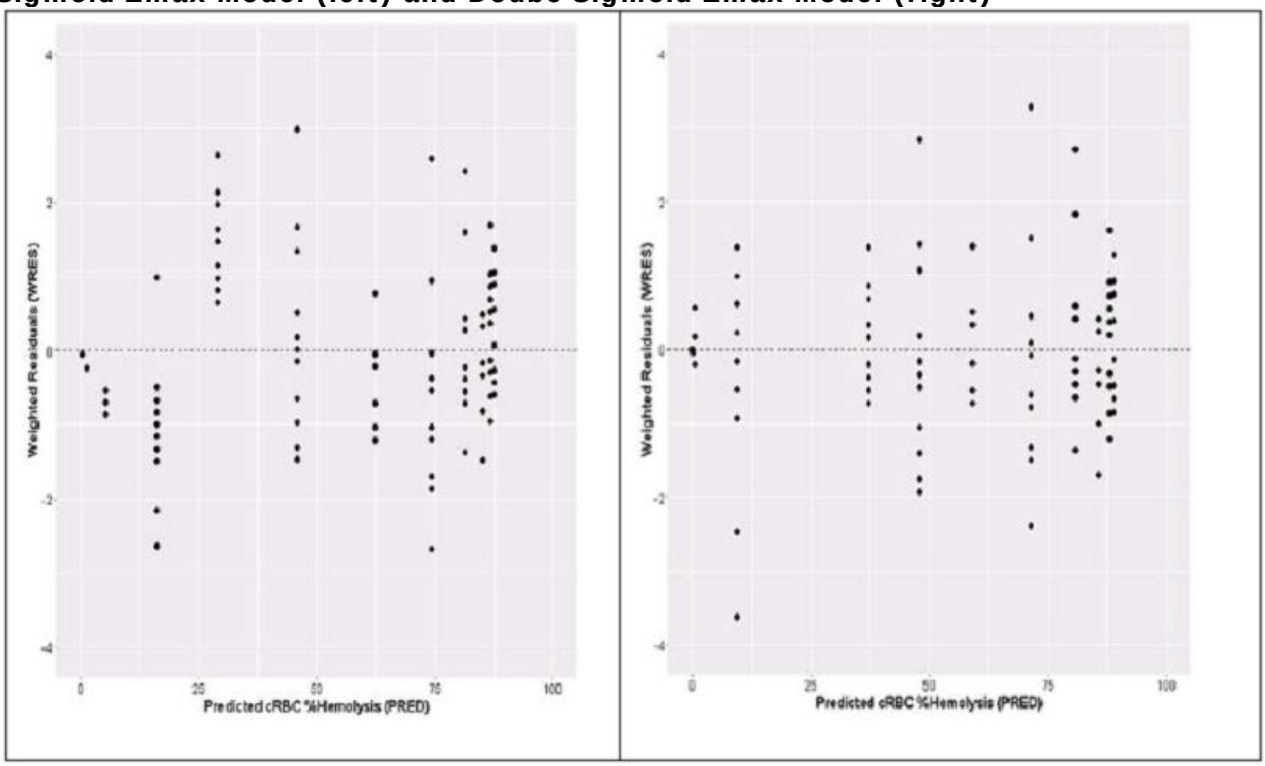
The analyses performed included Pop-PK analysis, Pop-PK/PD analysis (ie, free C5 for target engagement and cRBC haemolytic activity for proof of pharmacology), exploratory analysis of exposure response for efficacy and safety endpoints, and ADA/NAb measurement and analysis.

A model was developed to quantify the relationship between haemolysis and free C5 using in vitro data.

A single and double sigmoid maximum effect (Emax) models were tested. In this last model two different additive error terms were assigned, one for data <0.78 µg/mL free C5 concentration, and the other for data ≥ 0.78 µg/mL free C5 concentration, to reflect two different errors observed for these two ranges. Improvements in model fit are represented in Figure 5.

[7]Berrih-Aknin S, Le Panse R. Myasthenia gravis: A comprehensive review of immune dysregulation and etiological mechanisms. Journal of Autoimmunity 52 (2014) 90-100
[8]Kusner L, Kaminski HJ, Soltys J. Effect of complement and its regulation on myasthenia gravis pathogenesis. Expert Rev Clin Immunol 2008; 4(1): 43–52.
[9]Ha JC, Richman DP. Myasthenia gravis and related disorders: Pathology and molecular pathogenesis. Biochimica et Biophysica Acta 1852 (2015) 651–657

Figure 5 Weighted Residual Error versus Predicted cRBC% Haemolysis for Single Sigmoid Emax Model (left) and Doube Sigmoid Emax Model (right)



Abbreviations: C5 = complement component 5; cRBC = chicken red blood cell; E_{max} = maximum effect

A comparison of the minimum objective function value (MOFV) for the double and single sigmoid Emax models, 599 and 663, respectively, indicated the double sigmoid Emax model was statistically superior with a ΔMOFV of 64 units ($p<0.001$) compared to the single sigmoid Emax model.

Using the final model and parameter estimates for a haemolysis of 20%, the predicted free C5 concentration was 0.51 µg/mL.

The correlation between free C5 serum concentration and cRBC haemolysis activity was evaluated using data collected from an in vitro experiment and data from Study ECU-MG-301. Since the eculizumab dose targeted in clinical trials is at the asymptote of the maximal response, the in vivo data proved to be insufficient for developing a predictive model correlating free C5 serum concentration and cRBC haemolysis activity. The in vitro data are better for developing a model to predict the correlation between free C5 and cRBC % haemolysis.

2.3.4. Pharmacokinetic/Pharmacodynamic modelling

A Pop-PK model including an assay conversion factor, and haemolysis and free C5 (only from Study ECU-MG-301) exposure response analyses for eculizumab in patients with refractory gMG based on data from Studies C08-001 and ECU-MG-301. The analysis results with and without
Study C08-001 are essentially identical suggesting at the population level the impact of bioanalytical method differences does not influence the estimation of Pop-PK parameters with the non-linear correction factor applied to analyse the pooled data from Studies C08-001 and ECU-MG-301.

Exploratory efficacy and safety exposure response analyses were performed only for patients from
Study ECU-MG-301.The objectives of the modelling and simulation analyses were to support the eculizumab

dosing regimen in the Phase 3 Study ECU-MG-301 for treatment of patients with refractory gMG based on current knowledge of the underlying PK and exposure-response relationships for biomarkers, efficacy, and safety endpoints.

Table 2 Patients from Studies C08-001 and ECU-301 Included in the Population Pharmacokinetics and Exposure-Response Analyses by Protocol and Treatment

Study	Treatment	Patients	Patients pop PK analysis	Patients free C5 analysis	Patients hemolysis analysis	Patients efficacy analysis	Patients safety analysis
C08-001	Eculizumab-Placebo	14 *	13	0	13	0	0
ECU-MG-301	Eculizumab	62	62	62	62	62	62
	Placebo	63	0	0	0	63	63
Total Patients		139	75	62	75	125	125

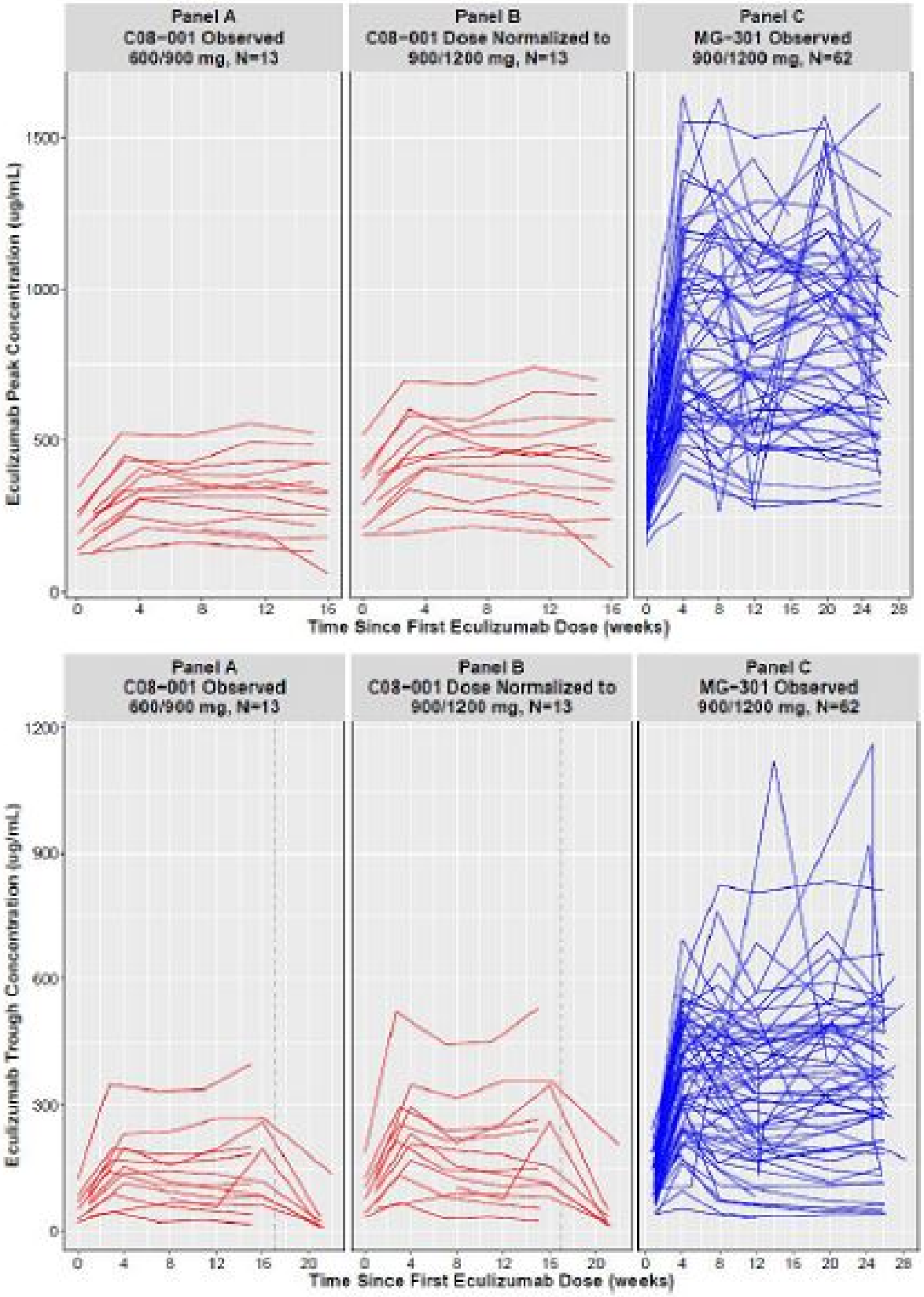
* Two patients dropped out before period 2, a total of 13 patients were treated with eculizumab and 13 patients were treated with placebo.
Sources: ALEX-PKPD-153_Create-E-R-nonmemdat-MG301.r, alx-pk-exploratory-analysis-20160907.R, Create_analset.sas, alx-ae-summary-table-20160831.R

Abbreviations: C5 = complement component 5; PK = pharmacokinetics; pop = population

Population Pharmacokinetics Analysis

The previously developed 1-compartment model with data from Study C08-001 with clearance and volume of distribution allometrically scaled by body weight was fitted to the pooled Studies C08-001 and ECU-MG-301 data. The eculizumab peak and trough concentrations-time profiles for the Phase 2 (Study C08-001) and Phase 3 (Study ECU-MG-301) trials are presented in Figure 6. Concentrations of Study C08-001 data were normalized to Study ECU-MG-301 dose levels. Median profiles for the two studies showed roughly a 2-fold difference at steady state.

Figure 6 Eculizumab Peak and Trough Concentrations Time Profiles Stratified By Study



Model development was carried out using first-order, conditional estimation with interaction. The two-compartment model with first order elimination, including body weight effects, was defined as the base

model and was the starting point for the covariate assessment. The eculizumab PK data were well-described by a 2-compartment model with 1st-order elimination. Final Pop-PK model parameter estimates are presented in Table 3 below. All PK parameters were allometrically scaled by body weight that allowed interindividual differences in the population of interest; in addition plasma exchange (PE) events were modelled to account for a temporary increase in eculizumab clearance during the PE period. There was approximately a twofold difference in the observed dose normalized eculizumab concentrations between Studies C08-001 and ECU-MG-301. One potential cause could be the change in assays which were used to analyse eculizumab concentrations from Studies C08-001 (method BTM-0056) and ECU-MG-301 (method 1727-112). A non-linear assay conversion factor was estimated to scale Study C08-001 exposures to the levels observed in Study ECU-MG-301. No other available covariates were found to influence eculizumab exposure. The effect of body weight on clearance expressed as the power coefficient is estimated at 1.32. This coefficient is larger than expected from allometric scaling principles and indicates that eculizumab clearance is substantially affected by body weight.

Table 3 Parameter Estimates of Final Population Pharmacokinetic Model

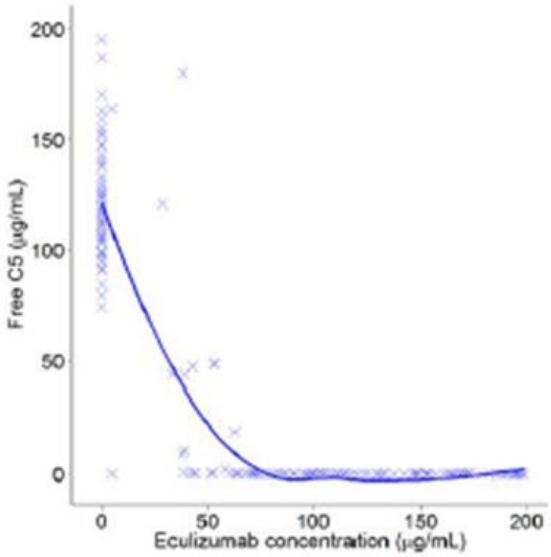
	Final model				Bootstrap	
Parameter	Estimate	95% CI	RSE (%)	Shrinkage (%)	Median	95% CI
CL (L/h)	0.00737	[0.00662-0.0082]	1.1		0.0073	[0.0067-0.00803]
V1 (L)	2.21	[1.94-2.53]	8.6		2.22	[1.87-2.47]
V2 (L)	2.4	[2.04-2.82]	9.5		2.37	[1.88-2.83]
Q (L/h)	0.182	[0.0733-0.454]	27.4		0.168	[0.0314-0.372]
Weight effect on CL/Q	1.32	[1.03-1.61]	11.4		1.34	[1.04-1.62]
Weight effect on V1/V2	0.634	[0.494-0.774]	11.3		0.641	[0.481-0.805]
PE effect on CL	11.2	[8.66-13.7]	11.4		11.2	[7.82-464]
Assay conversion factor	1.07	[1.05-1.09]	1		1.07	[1.05-1.1]
Interindividual Variability						
CL (CV%)	41.2	[33.1-48.3]	17.2	0.9	40.1	[32.5-48.3]
V1 (CV%)	24.1	[17.1-29.6]	25	7	23.2	[18.1-31]
Correlation CL-V1	0.0467	[0.0193-0.0741]	30		0.044	[0.0158-0.0743]
Residual Error						
Proportional error Ph3 (%)	39.9	[38.8-41]	2.9		39.8	[37.2-42.2]
Proportional error Ph2 (%)	27.1	[21.6-31.7]	18.8		26.2	[14.4-35.7]
Additive error Ph2 (ug/mL)	15.9	[10.2-21.6]	18.4		14.1	[5.53-29.5]

CI = confidence interval; RSE = relative standard error; CL=clearance; V1=volume of distribution in the central compartment; V2=volume of distribution in the peripheral compartment; Q = intercompartmental clearance; PE = plasma exchange. 1000 replicates were run for the bootstrap analysis.
Source: alx-pk-parameter-tab-bootstrap-final-20160804.R

Free Complement Component 5 Analysis

Figure 7 shows that only a very limited number of observations were available to define the slope of the curve relating free C5 and eculizumab concentrations. All observations come from Study ECU-MG-301.

Figure 7 Scatter Plot of Free C5 Concentration versus Eculizumab Concentration in Study ECU-MG-301



Observations within the 0-200 µg/mL Eculizumab concentration range, including a loess trend line.
Source: plot_freeC5.r

versus

The relationship between free C5 and eculizumab concentration could be described by an inhibitory sigmoid E_{max} model. The final IC_{50} estimate is in line with the binding kinetics between eculizumab and free C5, ie, one molecule of eculizumab would bind to 2 molecules of free C5.

Haemolysis Analysis

A higher percent of patients achieved complete inhibition of terminal complement (<20% cRBC haemolysis) in Study ECU-MG-301 (87%) compared to Study C08-001 (77%). The relation between percentage haemolysis and eculizumab concentration was best described with a sigmoid E_{max} function with shared interindividual variability between baseline haemolysis and IC_{50}. The model estimated IC_{50} and Hill factor were 40.8 µg/mL (RSE=3.1%) and 4.1 (RSE=5.4%), the corresponding IC_{95} and IC_{99} estimates were 83.6 and 124.9 µg/mL, respectively. Substantial uncertainty in the parameter estimations for IC_{50} and ω (shared IIV on E_0 and IC_{50}) was observed. This is likely due to the limited number of data points informing these parameters. Most observations are at the extremes, either at baseline or at full haemolysis inhibition.

Exposure- Response Analysis for Myasthenia Gravis Activities of Daily Living Profile, Quantitative Myasthenia Gravis Score for Disease Severity, and Myasthenia Gravis Composite Score in Study ECU-MG-301

With eculizumab treatment, Myasthenia Gravis Activities of Daily Living Profile (MG-ADL), Quantitative Myasthenia Gravis Score for Disease Severity (QMG), and Myasthenia Gravis Composite Score (MGC) change from baseline showed a greater decrease compared to placebo. Overall, there was no consistent evidence of increased efficacy with increased eculizumab exposure, compatible with the use of a therapeutic dose that sufficiently achieves full inhibition of terminal complement activation.

Exposure – Response Analysis for Clinical Deterioration

Clinical deterioration was reported in 23 of the 125 patients in Study ECU-MG-301. A total of 16/63 (25%) patients on placebo experienced one or more events of clinical deterioration while 7/62 (11%) patients on eculizumab had one or more events of clinical deterioration. The incidence of the first time to clinical deterioration between the low (below median area under the concentration-time curve [AUC] in Study ECU-MG-301) and high (above or equal to median AUC in Study ECU-MG-301) AUC bins are similar as indicated by the number of events in each of two bins, 3 and 4, respectively. These findings illustrate the absence of an exposure effect on time to clinical deterioration within the observed eculizumab exposure range in Study ECU-MG-301.

Exposure Safety Analysis

No relevant differences are observed between eculizumab and placebo treated patients as well as no trends are observed at increasing eculizumab exposure.

Anti-drug Antibodies

There were very limited ADA positive results and they occurred either in placebo treated patients (3 samples) or pre dose for an eculizumab treated patient (one sample) and all of them have low signal to noise (S/N) values. These ADA findings have no impact on Pop-PK or PK/PD analyses.

Pharmacokinetic/Pharmacodynamic and Exposure Response Simulations

Exposure-response simulations were used to establish target eculizumab concentrations achieving complete terminal complement inhibition for free C5 (116 ug/mL). Using the threshold value 0.5 µg/mL, which is predicted to produce 20% haemolysis, based on in vitro experiment data and model-based analysis, the target concentration of eculizumab was identified as 116 ug/mL. Dose simulations indicated the dose for Study ECU-MG-301 (900 mg/1200 mg) had a higher percent of patients (87%) exceeding the threshold target concentration than the dose for Study C08-001 (600 mg/900 mg) (78%), and was shown to be well-tolerated and to demonstrate clinical benefit in refractory gMG patients. The 900/1200 mg dose regimen is justified as the labelled dose for refractory gMG.

No data have been presented to establish that PD endpoints can be surrogates of the clinical responses. The presented data only indicate that the PD endpoints predicted a maximum response for the patients and most of the patients have shown clinical response.

2.3.5. Discussion on clinical pharmacology

No new clinical pharmacology studies have been conducted.

A Pop-PK analysis revealed that the PK of eculizumab depends on weight, and that it is best described by a two compartmental model. A non-linear correction factor was estimated for data from Study C08-001 since dose corrected plasma concentrations are lower than those from Study ECU-MG-301. The inclusion of data from Study C08-001 has been proved not to influence the results from the Pop-PK model.

The observed effect on free C5 was related to plasma concentrations by means of a sigmoid E_{max} model based on data from Study ECU-MG-301. The relationship revealed that in presence of eculizumab free C5 can fall to undetectable values. The estimated value of IC_{50} was 33.1 ug/mL.

The relationship between eculizumab plasma concentrations and the haemolysis was described by a Sigmoid E_{max} function. Data from the two studies mentioned before were used. Individual plasma concentrations estimated from the PK model were used, and in the final model corrected plasma concentrations from Study C09-001 were used. This model does not need further validation because it has been proven that the PK of

eculizumab is not influenced by the data from Study C08-001. There was no relationship between eculizumab exposure and MG-ADL, QMG, MGC (data from Study ECU-MG-301), or clinical deterioration.

Simulations based on the models developed for free C5 and haemolysis were used to establish target eculizumab concentration. This concentration was based on the model developed to describe the "in vitro" effect of eculizumab. The proposed target concentration is 116 ug/mL. However, because no relationship between free C5 levels and the therapeutic effect of eculizumab has been presented, the proposed target concentration should be interpreted with caution.

The justification of the dose selection for Phase 3 studies is based on the available data for the approved aHUS dosing regimen and the fact that at the at the selected dose regimen 87% of the patients achieved the concentration required for complete complement inhibition (<20% cRBC haemolysis), with 92% achieving free C5 concentration of <0.5 µg /mL No specific dose-response studies have been conducted for this indication and the lack of correlation between exposure and clinical effects does not exclude that other doses/regimen could also work.

2.3.6. Conclusions on clinical pharmacology

The PK of eculizumab has been properly characterized and the approach used to correlate exposure and studied PD endpoints seems reasonable. However, considering that no relationship between clinical response and exposure has been observed, and that PD endpoints do not correlate to the clinical response, the proposed target concentration should be interpreted with caution.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- *Long-term stability (LTS) programs are currently ongoing to cover storage of samples from Study ECU-MG-301. Stability data for eculizumab PK (assay IM-1727-112), free C5, and haemolytic long-term storage samples will be available following the final analysis in Q3-Q4 2017. The applicant should submit the stability data when available.*

2.4. Clinical efficacy

The submission related to the refractory gMG clinical development program included 1 ongoing and 2 completed clinical studies (Table 1):

• A randomized, double-blind, placebo-controlled, multicenter Phase 3 study (Study ECU-MG-301; completed)

• A Phase 3, open-label, multicenter extension study of Study ECU-MG-301 (Study ECU-MG-302; ongoing)

• A randomized, double-blind, placebo-controlled, multicenter crossover Phase 2 study (Study C08-001; completed)

The data from Study ECU-MG-301 represent the main proof of efficacy of Soliris in the intended indication. Maintenance of the effect is based also on preliminary data from Study ECU-MG-302 with an intended duration of 4 years.

2.4.1. Dose response studies

No specific dose-response studies have been conducted for this indication. The proposed dosing regimen for the treatment of refractory gMG is 900 mg weekly for 4 weeks followed by 1200 mg for the 5th dose and then every two weeks. This dose is identical to that approved for the treatment of aHUS. Pharmacokinetic (PK)/

Pharmacodynamic (PD) modelling and Pop-PK/PD analysis performed with data from Studies ECU-MG-301 and C08-001 showed that at the selected dose 87% of the patients achieved the concentration required for complete complement inhibition(<20% cRBC haemolysis), with 92% achieving free C5 concentration of <0.5 µg /mL. The figures for 600/900 doses were 75% and 77%, respectively.

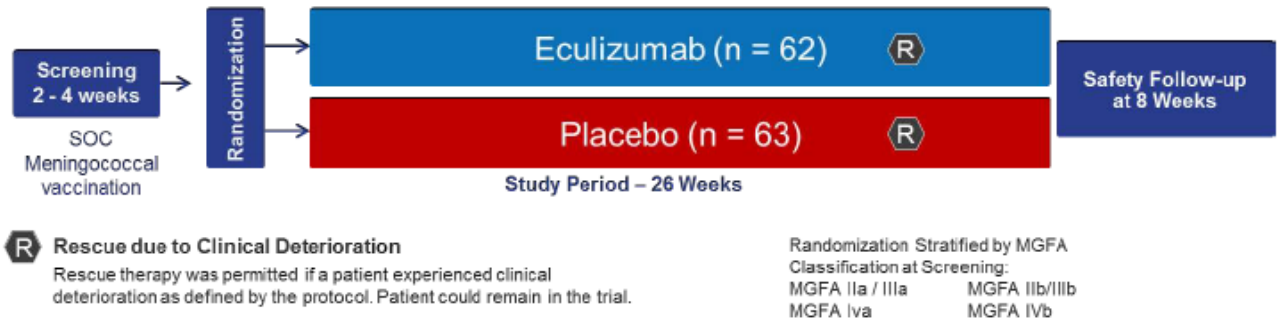
2.4.2. Main study(ies)

2.4.2.1. Study ECU-MG-301

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Eculizumab in Subjects with Refractory Generalised Myasthenia Gravis (gMG)

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter trial to evaluate the safety and efficacy of eculizumab for the treatment of patients with refractory gMG. There were 3 periods in this study: Screening Period, Study Period, and Follow-up Period (for patients who withdrew from this study or who did not enter the extension study). After completing the 26-week Study Period, patients were provided the opportunity to enter an extension study (Study ECU-MG-302) to receive open-label eculizumab.

Figure 8 Study Design ECU-MG-301



Abbreviations: MGFA = Myasthenia Gravis Foundation of America; SOC = standard of care

Methods

- **Study participants**

Inclusion criteria

1. Male or female patients ≥18 years of age

2. Diagnosis of MG by the following tests:

    a. Positive serologic test for anti-AChR Abs as confirmed at Screening, and

    b. One of the following:

        i. History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation;

        ii. History of positive anticholinesterase test (eg, edrophonium chloride test); or

        iii. Patient demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating physician

3. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV at Screening

4. MG-ADL total score ≥6 at Screening and at Randomization (Day 1)

5. Patients who had the following:

a. Failed treatment over 1 year or more with 2 or more immunosuppressive therapies (ISTs) (either in combination or as monotherapy) (ie, continued to have impairment of activities of daily living (ADL) [persistent weakness, experienced crisis, or unable to tolerate IST] despite ISTs); or

b. Failed at least 1 IST and required chronic plasmapheresis, PE, or IVIg to control symptoms (ie, patients who required PE or IVIg on a regular basis for the management of muscle weakness at least every 3 months over the previous 12 months)

i. Immunosuppressive therapies included, but were not limited to, corticosteroids, AZA, mycophenolate mofetil (MMF), methotrexate (MTX), CYC, tacrolimus (TAC), or cyclophosphamide

6. If patients who entered the study were receiving IST, they were required to have been on the IST for ≥6 months (for AZA and on a stable dose for ≥2 months prior to Screening) or for ≥3 months for other ISTs (ie, MMF, MTX, CYC, TAC, or cyclophosphamide; and on a stable dose for ≥2 months).

7. If patients who entered the study were receiving oral corticosteroids, they were required to have been on a stable dose for ≥4 weeks (ie, 28 days) prior to Screening.

8. If patients who entered the study were receiving a cholinesterase inhibitor, they were required to be on a stable dose for ≥2 weeks prior to Screening.

Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. History of thymoma or other neoplasms of the thymus

2. History of thymectomy within 12 months prior to Screening

3. Weakness only affecting ocular or periocular muscles (MGFA Class I)

4. Myasthenic crisis at Screening (MGFA Class V)

5. Pregnancy or lactation

6. Any systemic bacterial or other infection that was clinically significant in the opinion of the Investigator and had 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 study or exposure to other investigational agent, device, or procedures within 30 days prior to Screening

12. Previous treatment with eculizumab

13. Hypersensitivity to murine proteins or to 1 of the excipients of eculizumab

14. Any medical condition that, in the opinion of the Investigator, might have interfered with the patient's participation in the study, posed any added risk for the patient, or confounded the assessment of the patient

- **Treatments**

Eculizumab (600 mg, 900 mg, or 1200 mg) or matching placebo was administered intravenously over approximately 35 minutes (range: 25 to 45 minutes) according to the following regimen (**Table 4** below):

Table 4 Treatments Administered in Study ECU-MG-301

Dose Period	Frequency of Study Drug Administration	Visits	Number 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 sixth dose onward	7–17	4	1200 mg
Supplemental Doses	If plasmapheresis/PE was given due to clinical deterioration, supplemental doses were administered within 60 minutes after the end of each plasmapheresis/PE session.		2	600 mg

Abbreviations: PE = plasma exchange

The overall study duration for an individual patient was up to 38 weeks, including Screening and Follow-up (8 weeks after the last dose of study drug for patients who discontinued the study, or for patients who completed the study but did not enrol in the extension study). The total treatment time was 26 weeks.

Patients could continue to receive stable dose/type of IST, but no new ISTs and no changes in IST dosage were permitted during the study without Sponsor approval. Patients were not permitted to enter the study while receiving rituximab or regular IVIg or PE therapy.

Due to its mechanism of action, the use of Soliris increases the patient's susceptibility to meningococcal infection (*Neisseria meningitidis* [*N. meningitidis]*). Meningococcal disease due to any serogroup may occur. Patients were vaccinated against *N. meningitidis*, if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer or vaccinated according to current medical/country guidelines.

Rescue therapy was permitted for patients experiencing protocol-defined MG clinical deterioration defined as a patient experiencing 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 (ie, talking, chewing, swallowing, breathing, upper and lower extremity weakness): To Grade 3, or 2-point worsening; (3) the treating physician believes that the patient's health is in jeopardy if rescue therapy is not given.

- **Objectives**

Primary Objective: The primary objective was to assess the efficacy of eculizumab, as compared with placebo, in the treatment of refractory gMG based on the improvement in the MG-ADL total score.

Secondary Efficacy Objectives: The secondary efficacy objectives were:

- Characterize the overall safety and tolerability of eculizumab as compared with placebo in refractory gMG patients

- Assess the efficacy of eculizumab as compared with placebo by the following additional disease-specific efficacy measures:
  - QMG total score
  - MGC total score
  - Improvement in primary symptoms that are most clinically meaningful to the patients
- Characterize the effect of eculizumab as compared with placebo on quality of life measures
- Describe the PK and PD of eculizumab in refractory gMG patients

- **Outcomes / endpoints**

- **Outcomes**

Myasthenia Gravis Activities of Daily Living Profile: The MG-ADL scale is a validated 8-item patient-reported outcome measure. For the MG-ADL, the patient assesses their functional disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb impairment (2 items) over the prior 7 days. These 8 items are not weighted and are individually graded from 0 (normal) to 3 (most severe), providing a total MG-ADL score ranging from 0 to 24 points. A 2-point reduction in MG-ADL total score is considered a clinically meaningful improvement (Muppidi, 2011). A ≥3-point improvement in MG-ADL total score from Baseline at Week 26 was selected as a robust clinically significant threshold for the secondary endpoint.

Quantitative Myasthenia Gravis Score for Disease Severity: The QMG is a validated direct physician assessment scoring system that 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 item is graded from 0 (normal) to 3 (most severe), providing a total QMG score ranging from 0 to 39 points. A 3.5-point difference has been shown to correlate with clinically meaningful change (Zinman, 2007; Barth, 2011). A ≥5-point improvement in QMG total score from Baseline at Week 26 was selected as a robust clinically significant threshold for the secondary endpoint.

Myasthenia Gravis Composite Score: The MGC score is a validated outcome measure for evaluating the symptoms and signs of MG (Burns, 2010). Possible cumulative scores range from 0 to 50, with higher scores representing greater morbidity. A 3-point improvement in score has been shown to correlate with improvement that is meaningful to the patient (Burns, 2012).

Quality of Life Assessments

- *Myasthenia Gravis Quality of Life 15-item Scale (MG-QoL15)*: The MG-QoL15 is a validated disease-specific questionnaire (Burns, 2010) consisting of 15 questions with responses to each questioned scored from 0 (not at all) to 4 (quite a bit), and possible cumulative scores ranging from 0 to 60, with higher scores representing worse quality of life as assessed over a recall period of the prior 4 weeks. Previous studies (Burns, 2010; Barnett, 2013) have suggested that a 7- to 8-point improvement in the MG-QoL15 score is indicative of treatment impact.
- *Quality of Life in Neurological Disorders Fatigue Scale (Neuro-QoL Fatigue)*: The Neuro-QoL Fatigue is a validated brief 19-item survey of fatigue, completed by the patient (Cella, 2010). The Neuro-QoL Fatigue scale was specifically incorporated to characterize the impact of MG-related fatigue in the refractory gMG patient. Higher scores indicate greater fatigue and greater impact of MG on activities.
- European Quality of Life Health 15-item Questionnaire (EQ-5D): The EQ-5D consists of a 5-item questionnaire and a visual analogue scale (EQ-VAS). The 5 questions pertain to: mobility, self-care,

usual activities, pain/discomfort, and anxiety/depression (Szende, 2004). Each question, or dimension, has 3 levels: no problems, some problems, or extreme problems. The EQ-VAS records the patient's perceptions of their current, overall health status.

Other Efficacy outcomes

- *Negative Inspiratory Force (NIF) and Forced Vital Capacity (FVC):* Measurement of FVC, as 1 of the test items in the QMG, was completed when the QMG was administered. Measurement of NIF was completed using the NIF meter and is a non-invasive index of diaphragm strength.
- *Myasthenia Gravis Foundation of America Post-Interventional Status (MFGA-PIS):* The MGFA-PIS is a disease-specific outcome measure, which provides the physician's global assessment of the patient's clinical status (ie, response to therapy) following initiation of MG treatment. The change is recorded in status categories relative to Baseline of improved, unchanged, worse, exacerbation, and died of MG.
- *Clinical Deterioration:* Sites were required to evaluate the patient's reporting of clinical deterioration as soon as possible and within 48 hours of their notifying the Investigator of the symptom onset. Clinical deterioration was defined as follows:
  - An MG crisis, which was defined as weakness from MG that was severe enough to necessitate intubation or to delay extubation following surgery, and for whom respiratory failure was due to weakness of respiratory muscles. Severe bulbar (oropharyngeal) muscle weakness may have accompanied the respiratory muscle weakness, or may have been the predominant feature in some patients;
  - Significant symptomatic worsening to a score of 3 or a 2-point worsening on any 1 of the individual MG-ADL items other than double vision or eyelid droop; or
  - Patients for whom the Investigator believed that the patient's health was in jeopardy if rescue therapy was not given (eg, emergent situations).

Biomarker: Blood samples for the assays of AChR Abs were collected.

- **Efficacy Endpoints**

Primary Endpoint

- Change from Baseline in the MG-ADL total score at Week 26 of the Study Period for eculizumab compared with placebo.

Secondary Endpoints (hierarchical)

- Change from Baseline in the QMG total score at Week 26
- Proportion of patients with ≥3-point reduction in the MG-ADL total score from Baseline to Week 26 and with no rescue therapy
- Proportion of patients with ≥5-point reduction in the QMG total score from Baseline to Week 26 and with no rescue therapy
- Change from Baseline in the MGC scale total score at Week 26
- Change from Baseline in the MG-QoL15 at Week 26

Tertiary Endpoints

- Time to response as measured by the reduction in the MG-ADL total score (3-point reduction from Baseline)
- Change from Baseline in *Neuro-QoL Fatigue* at Week 26
- Change from Baseline in the EQ-5D at Week 26
- Change from Baseline in NIF at Week 26 in patients with abnormal NIF at Baseline
- Change from Baseline in FVC at Week 26 in patients with abnormal FVC at Baseline
- Change from Baseline in the MG-ADL individual items and changes from Baseline in the bulbar (items 1, 2, and 3), respiratory (item 4), limb (items 5 and 6), and ocular (items 7 and 8) MG-ADL subcategories at Week 26 in patients with an abnormal baseline score for the particular item or subcategory
- Change from Baseline in the MGFA-PIS at Week 26

- **Sample size**

The planned sample size of approximately 92 patients (46 assigned to eculizumab and 46 assigned to placebo) provided 90% power to detect a treatment difference at 26 weeks for both ADL and the QMG total scores. Actual enrolment totalled 125 patients.

- **Randomisation**

Patients were randomised on Day 1 on a 1:1 basis to the eculizumab arm or the placebo arm.

The randomisation was stratified according 4 MGFA classes of (a) IIa/IIIa; (b) IVa; (c) IIb/IIIb or (d) IVb.

- **Blinding (masking)**

All study patients, investigational site personnel, Alexion staff, Alexion designees, and all staff directly associated with the conduct of the study were blinded to the patient treatment assignments. If unblinding was deemed necessary by the Investigator, the Investigator could unblind the patient's treatment allocation using IXRS.

- **Statistical methods**

Analysis Populations

Full Analysis Set (FAS): All patients who were randomly assigned to study drug and who received at least 1 dose of study drug (eculizumab or placebo treatment), had a valid baseline assessment in the MG-ADL total score, and had at least 1 efficacy assessment after study drug infusion.

Per-Protocol (PP) Set: FAS patients who had no major protocol deviations.

Safety Set: All patients who received at least 1 dose of study drug (eculizumab or placebo).

Efficacy:

Efficacy analyses were performed on the FAS as well as the PP Set. The primary efficacy analysis was conducted on the available 26-week data from the Study Period for all patients. The trial was considered to have met its primary efficacy objective if a statistically significant difference ($p \leq 0.05$) between the eculizumab arm and the placebo arm was observed for the change from Baseline in the MG-ADL total score at Week 26. Confidence intervals (CIs) and p-values are presented.

For the primary analysis concerning the change from Baseline in the MG-ADL total score at Week 26, treatment arms were compared using a Worst-Rank analysis of covariance (ANCOVA) with effects for treatment. The Baseline MG-ADL total score and the randomization stratification variable were also covariates in the model.

Sensitivity analyses of the primary efficacy endpoint included the following:

• Worst-Rank ANCOVA sensitivity, using the change from Baseline to rescue/discontinuation for ranking patients in the rescue cohort, rather than days from initiation of treatment to time of rescue/discontinuation;

• Week 26 ANCOVA change from Baseline accounting for treatment arm, Baseline score, and randomisation stratification variable;

• Repeated Measures over time accounting for treatment arm, Baseline score, randomisation stratification variable, and visit; and

• Repeated Measures over time accounting for treatment arm, Baseline score, randomisation stratification variable, visit, and IST impact.

Secondary efficacy analyses used the available 26-week data from the Study Period unless otherwise specified.

The secondary endpoints involving changes from Baseline (ie, the QMG first secondary endpoint, the MGC fourth secondary endpoint, and the MG-QoL15 fifth secondary endpoint) were analysed using a Worst- Rank ANCOVA. The same array of sensitivity analyses for QMG total score, MGC total score, and MG-QoL15 total score were performed as were undertaken for the primary efficacy endpoint.

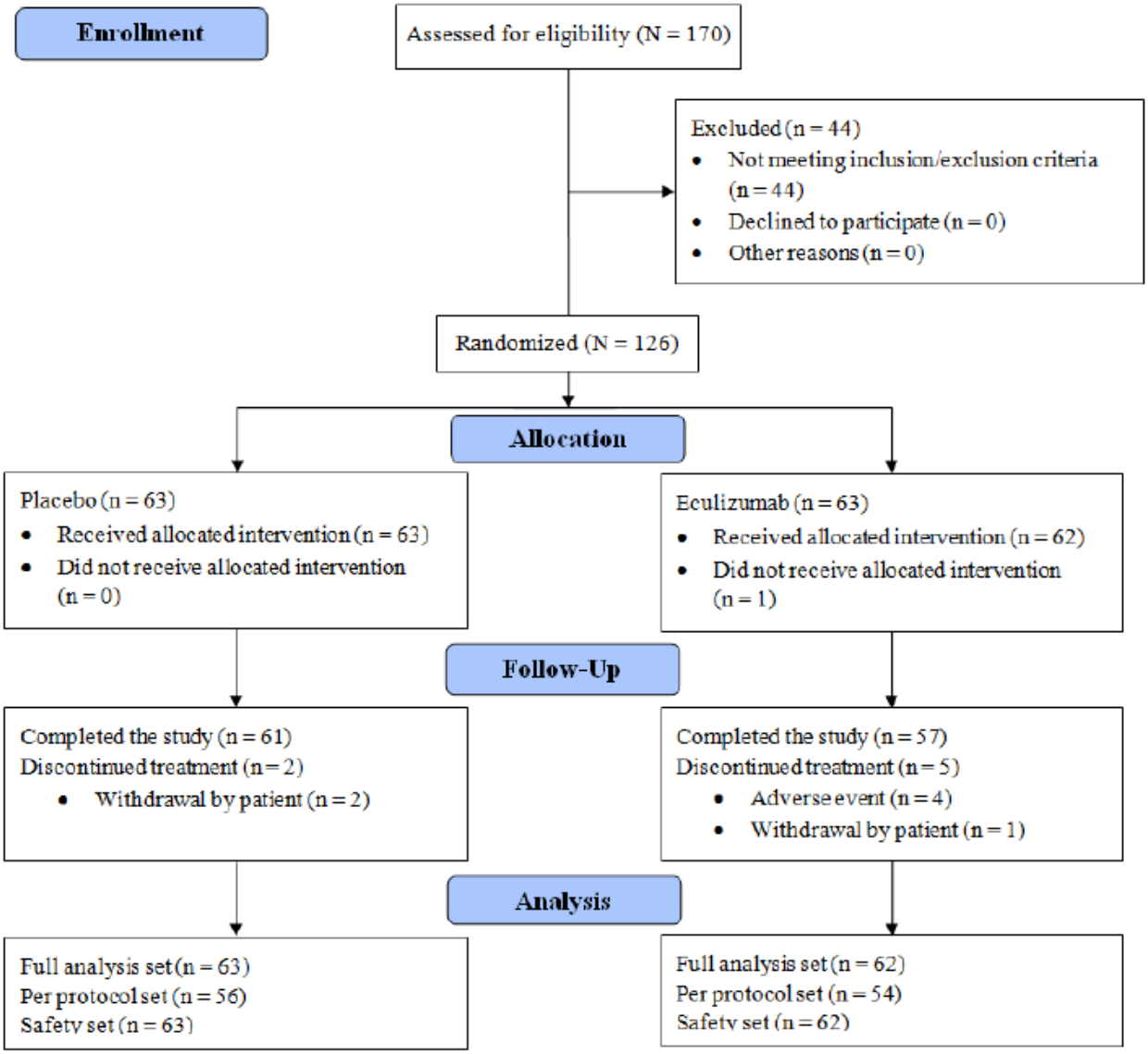
The secondary endpoints involving responder rates (ie, the proportion of patients with at least a 3-point reduction in the MG-ADL total score, the second secondary endpoint, and the proportion of patients with at least a 5-point reduction in the QMG total score, the third endpoint) were analysed by the Cochran-Mantel-Haenszel (CMH) test stratified by pooled randomisation stratification variable in order to compare eculizumab versus placebo.

Results

- **Participant flow**

A total of 170 patients were screened, of whom 44 were screen failures. The remaining 126 patients were randomly assigned to treatment, and 125 patients were treated; 1 patient who was randomly assigned to the eculizumab arm was randomized in error and never received study drug.

Figure 9. Study ECU-MG-301 - Diagram of Patient Disposition and Follow-Up



- **Recruitment**

The study was conducted at 114 centers in North America, South America, Europe, Australia, Japan, and South Korea, of which 76 enrolled and treated patients.

Date first patient enrolled: 30 Apr 2014

Date last patient completed: 19 Feb 2016

- **Conduct of the study**

Changes in the Conduct of the Study

The original protocol, dated 15 Aug 2013, was globally amended once during the study (Protocol Version 2.0, dated 13 Jun 2014).

- Extended the Follow-up Period to 8 weeks based on PK characteristics and to align Study ECU-MG-301 protocol with other ongoing eculizumab studies that also have an 8-week Follow-up Period.
- Modified exclusion criteria #8 and 9 (the washout period for IVIg and PE) from 4 weeks prior to Screening to 4 weeks prior to Randomisation. Consequently, the inclusion criterion #4 was modified to ensure that patients must have continued to meet the MG-ADL total score of ≥6 at Screening and at Randomisation.
- Revised the unblinding requirement to specify that the emergency unblinding of the patient's treatment allocation as the sole responsibility, and at the discretion of, the Investigator, and that Alexion must not have interfered with this decision.
- Provided clarifications on the responsibilities of the Investigator and Clinical Evaluator for the MG assessments to be performed in this study.
- Clarified that reporting of nonserious adverse events (AEs) was to start following the first dose of study drug infusion and reporting of serious adverse events (SAEs) was to start following the patient signing the informed consent form (ICF).
- Updated the protocol with a number of administrative changes, corrected typographical errors, and made minor grammatical changes for clarity.

Review of Inconsistent Data Entries for Key Parameters Related to MG Clinical Deterioration

The database was initially locked on 15 Apr 2016. After database lock, it was noted that 4 patients in the study had inconsistent data entries for key parameters related to MG clinical deterioration, including the use of rescue medication. These findings prompted unlocking of the database on 22 Apr 2016, followed by a review of data to ascertain whether all clinical deteriorations and rescue medications used had been appropriately captured for each patient. The database was relocked on 01 Jun 2016.

Four approaches were taken to verify the clinical deterioration and rescue medication data:

1. Review of existing patients with a reported clinical deterioration evaluation record, including rescue medication use and protocol criteria for the clinical deterioration event (n = 19 patients)

2. Review of all medication potentially indicative of worsening gMG (n = 22 patients)

3. Review of MG-ADL data for changes meeting the protocol criterion for clinical deterioration (n = 11 patients)

4. Review of all reported AE terms potentially indicative of worsening of gMG (n = 25 patients)

Specific records in the clinical database were unlocked for a total of 7 patients to address the identified inconsistencies. Each inconsistency that was identified was addressed with the site's Investigator using the electronic data capture system.

Changes in the Planned Analyses

The final statistical analysis plan (SAP) (Version 3.0) was signed on 23 Sep 2015.

The majority of patients had baseline classifications of MGFA IIa/IIIa or MGFA IIb/IIIb. Very few patients entered the study with Baseline MGFA Classification of IVa or IVb. In the eculizumab arm, there were 4 patients classified as MGFA IVa and 3 patients classified as MGFA IVb. Likewise, in the placebo arm, there were 2 patients classified as MGFA IVa and 3 patients as MGFA IVb. Since so few patients were in the MGFA IVa and IVb strata, modelling with the original 4 categories of the randomization stratification variable produces non-robust and biased estimated of least squares (LS) means and standard errors for those means. As a result, appropriate pooling of the randomisation stratification variable was employed for all of

the analyses. From a medical standpoint, the MGFA Class IVa stratum was pooled with the MGFA IIa/IIIa strata.

Likewise, the MGFA Class IVb stratum was pooled with the MGFA IIb/IIIb strata.

Protocol Deviations

Critical deviations occurred in 1 patient from each treatment arm.

- One (1.6%) patient from the placebo arm experienced a study procedure deviation. A patient had not received a meningococcal vaccination at Screening, and had been vaccinated for pneumococcus by mistake.
- One (1.6%) patient from the eculizumab arm experienced an eligibility and entry criteria deviation. A patient had a medical history event (thymectomy with thymoma) not noted during Screening and was taking concomitant pyridostigmine bromide without documentation of whether the dose was stable, as required by the study protocol.

Major protocol deviations occurred in 62 (49.2%) patients overall (24 [38.1%] patients in the placebo arm and 38 [60.3%] patients in the eculizumab arm).

Only patients who had major protocol deviations that could impact efficacy assessments were excluded from the PP Set.

Minor protocol deviations occurred in 46 (73.0%) patients in the placebo arm and 49 (77.8%) patients in the eculizumab arm, most of which were study procedure, laboratory evaluation, visit schedule, or investigational product deviations.

- **Baseline data**

There were no differences between treatment arms in the demographic characteristics of gender, age at first dose of study drug, ethnicity, weight, height, or BMI (see Table 5 and 6).

Table 5 Study ECU-MG-301 Demographics and Baseline Characteristics – Full Analysis Set

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)
Ethnicity				
Hispanic or Latino	n (%)	10 (15.9)	8 (12.9)	18 (14.4)
Not Hispanic or Latino	n (%)	50 (79.4)	51 (82.3)	101 (80.8)
Not Reported	n (%)	0 (0.0)	2 (3.2)	2 (1.6)
Unknown	n (%)	3 (4.8)	1 (1.6)	4 (3.2)
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)
Multiple	n (%)	0 (0.0)	1 (1.6)	1 (0.8)
Unknown	n (%)	0 (0.0)	1 (1.6)	1 (0.8)
Other	n (%)	2 (3.2)	4 (6.5)	6 (4.8)
Is the patient 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)
Region				
North America	n (%)	25 (39.7)	21 (33.9)	46 (36.8)
South America	n (%)	7 (11.1)	5 (8.1)	12 (9.6)
Europe	n (%)	18 (28.6)	33 (53.2)	51 (40.8)
Asia-Pacific	n (%)	5 (7.9)	0 (0.0)	5 (4.0)
Japan	n (%)	8 (12.7)	3 (4.8)	11 (8.8)
Weight (kg)	n	63	62	125
	Mean (SD)	86.24 (28.072)	87.67 (28.190)	86.95 (28.026)
	Median	83.10	80.00	80.70
	Min, Max	37.0, 155.5	42.9, 173.6	37.0, 173.6
Height (cm)	n	63	62	125
	Mean (SD)	167.07 (9.383)	166.63 (9.684)	166.85 (9.497)
	Median	167.50	165.10	166.70
	Min, Max	139.7, 184.2	150.1, 186.2	139.7, 186.2
BMI (kg/m^2) (2)	n	63	62	125
	Mean (SD)	30.53 (8.373)	31.37 (8.997)	30.94 (8.663)
	Median	30.67	30.15	30.67
	Min, Max	17.5, 51.1	14.8, 52.6	14.8, 52.6
MGFA Class at Screening				
Class IIa	n (%)	15 (23.8)	10 (16.1)	25 (20.0)
Class IIb	n (%)	14 (22.2)	8 (12.9)	22 (17.6)
Class IIIa	n (%)	16 (25.4)	20 (32.3)	36 (28.8)
Class IIIb	n (%)	13 (20.6)	17 (27.4)	30 (24.0)
Class IVa	n (%)	2 (3.2)	4 (6.5)	6 (4.8)
Class IVb	n (%)	3 (4.8)	3 (4.8)	6 (4.8)
MGFA Class Randomization Stratification				
Class IIa or IIIa	n (%)	32 (50.8)	30 (48.4)	62 (49.6)
Class IVa	n (%)	2 (3.2)	4 (6.5)	6 (4.8)
Class IIb or IIIb	n (%)	26 (41.3)	25 (40.3)	51 (40.8)
Class IVb	n (%)	3 (4.8)	3 (4.8)	6 (4.8)

Note: Region is defined as follows: North America – United States of America and Canada; South America – Argentina and Brazil; Europe – Belgium, Denmark, Spain, Finland, United Kingdom, Italy, Netherlands, Sweden, Czech Republic, Hungary, and Turkey; Asia-Pacific – Korea, Japan – Japan.
(1) Age = (Date of First IP Dose – Date of Birth) / 365.25
(2) BMI (kg/m2) = Weight (kg) / [Height (cm) / 100]2
Abbreviations: BMI = body mass index; IP = investigational product; Max = maximum; MGFA = Myasthenia Gravis Foundation of America; Min = minimum

The most common conditions reported as medical history in the overall study population (FAS) were hypertension (HTN [53]; essential HTN [2]), which was reported in 55 (44.0%) patients overall; this was followed by diabetes mellitus (DM [17]; type 2 DM [16]), reported in 33 (26.4%) patients overall; depression, reported in 31 (24.8%) patients overall; osteoporosis/osteopenia (osteoporosis [20]; osteopenia [10]; decreased bone density [1]), reported in 31 (24.8%) patients overall; oesophageal disease (gastroesophageal reflux disease [GERD] [21]; dyspepsia [4]; Barrett's oesophagus [2]; esophagitis [1]), reported in 28 (22.4%) patients overall; headache (migraine [12]; headache [11]; migraine without aura [1]), reported in 24 (19.2%) patients overall; and chronic obstructive pulmonary disease (COPD)/asthma (asthma [17]; COPD [6]; emphysema [1]), reported in 24 (19.2%) patients overall.

The most common surgical history reported by patients in the FAS is thymectomy (68 [54.4%] patients overall; 31 [49.2%] patients in the placebo arm and 37 [59.7%] patients in the eculizumab arm).

Table 6 Study ECU-MG-301 Myasthenia Gravis History – Full Analysis Set

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Total (N = 125)
Age at MG Diagnosis (years) (1)	n	63	62	125
	Mean (SD)	38.12 (19.553)	38.02 (17.839)	38.07 (18.647)
	Median	32.60	32.65	32.60
	Min, Max	7.7, 78.0	5.9, 70.8	5.9, 78.0
Duration of MG (years) (2)	n	63	62	125
	Mean (SD)	9.23 (8.405)	9.87 (8.108)	9.55 (8.232)
	Median	6.80	7.00	6.90
	Min, Max	1.0, 33.8	1.3, 29.7	1.0, 33.8
Maximum MGFA Clinical Classification Since Diagnosis Prior to Screening				
Class II	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Class IIa	n (%)	6 (9.5)	4 (6.5)	10 (8.0)
Class IIb	n (%)	6 (9.5)	4 (6.5)	10 (8.0)
Class III	n (%)	0 (0.0)	1 (1.6)	1 (0.8)
Class IIIa	n (%)	9 (14.3)	9 (14.5)	18 (14.4)
Class IIIb	n (%)	10 (15.9)	9 (14.5)	19 (15.2)
Class IV	n (%)	0 (0.0)	4 (6.5)	4 (3.2)
Class IVa	n (%)	10 (15.9)	7 (11.3)	17 (13.6)
Class IVb	n (%)	13 (20.6)	13 (21.0)	26 (20.8)
Class V	n (%)	9 (14.3)	11 (17.7)	20 (16.0)
Has patient ever required ventilatory support?				
Yes	n (%)	14 (22.2)	15 (24.2)	29 (23.2)
No	n (%)	49 (77.8)	47 (75.8)	96 (76.8)
Any MG exacerbation including crisis?				
Yes	n (%)	53 (84.1)	52 (83.9)	105 (84.0)
No	n (%)	10 (15.9)	10 (16.1)	20 (16.0)
Total Number of Patients with Exacerbations	n (%)	52 (82.5)	46 (74.2)	98 (78.4)
Total Number of Reported Exacerbations	n	316	206	522
Total Number of Patients with MG Crisis	n (%)	10 (15.9)	13 (21.0)	23 (18.4)
Total Number of Reported MG Crises	n	25	24	49
Any hospitalizations for MG since diagnosis?				
Yes	n (%)	48 (76.2)	47 (75.8)	95 (76.0)
No	n (%)	15 (23.8)	15 (24.2)	30 (24.0)
Any hospitalizations for MG in the past 2 years?				
Yes	n (%)	29 (46.0)	30 (48.4)	59 (47.2)
No	n (%)	34 (54.0)	32 (51.6)	66 (52.8)
Total number of hospitalizations for MG in past 2 years	n	63	62	125
	Mean (SD)	1.5 (2.51)	1.6 (3.08)	1.5 (2.79)
	Median	0.0	0.0	0.0
	Min, Max	0, 12	0, 21	0, 21
	Total	95	97	192
MG-ADL total score at Baseline	n	63	62	NC
	Mean (SD)	9.9 (2.58)	10.5 (3.06)	NC
	Median	9.0	10.0	NC
	Min, Max	5, 18	5, 18	NC
QMG total score at Baseline	n	63	62	NC
	Mean (SD)	16.9 (5.56)	17.3 (5.10)	NC
	Median	16.0	17.0	NC
	Min, Max	8, 34	6, 31	NC
MGC total score at Baseline	n	63	62	NC
	Mean (SD)	18.9 (5.95)	20.4 (6.13)	NC
	Median	19.0	21.0	NC
	Min, Max	7, 40	7, 35	NC
MG-QoL15 total score at Baseline	n	63	62	NC
	Mean (SD)	30.7 (12.72)	33.6 (12.21)	NC
	Median	31.0	33.5	NC
	Min, Max	6, 60	6, 59	NC

(1) Age at MG Diagnosis = (Date of MG Diagnosis – Date of Birth) / 365.25
(2) Duration of MG = (First Dose Date – MG Diagnosis Date) / 365.25

Abbreviations: Max = maximum; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGC = Myasthenia Gravis Composite score; MGFA = Myasthenia Gravis Foundation of America; MG-QoL15 = Myasthenia Gravis Quality of Life 15-item scale; Min = minimum; NC = not calculated; QMG = Quantitative Myasthenia Gravis score for disease severity

Treatments and Medications

Patients in this study had either failed 2 or more ISTs or had used IVIg, or both. Over half of the total patients had tried or failed at least 3 concomitant ISTs and the majority had tried or failed IVIg.

Table 7 Immunosuppressant Therapies, Intravenous Immunoglobulins, and Plasma Exchange Used Prior to Study Treatment in Study ECU-MG-301 – Safety Set

MG Treatment, n (%)	Placebo (N = 63)	Eculizumab (N = 62)	Total (N = 125)
Corticosteroids	62 (98.4)	58 (93.5)	120 (96.0)
Azathioprine	47 (74.6)	47 (75.8)	94 (75.2)
Mycophenolate Mofetil	29 (46.0)	27 (43.5)	56 (44.8)
Cyclosporine	18 (28.6)	18 (29.0)	36 (28.8)
Tacrolimus	11 (17.5)	9 (14.5)	20 (16.0)
Methotrexate	8 (12.7)	6 (9.7)	14 (11.2)
Rituximab	7 (11.1)	7 (11.3)	14 (11.2)
Cyclophosphamide	3 (4.8)	3 (4.8)	6 (4.8)
Patients using Only 2 ISTs	28 (44.4)	30 (48.4)	58 (46.4)
Patients using Only 3 ISTs	19 (30.2)	20 (32.3)	39 (31.2)
Patients using 4 or more ISTs	15 (23.8)	11 (17.7)	26 (20.8)
IVIg	48 (76.2)	51 (82.3)	99 (79.2)
Plasma Exchange	29 (46.0)	31 (50.0)	60 (48.0)

Abbreviations: IST = immunosuppressive therapy; IVIg = intravenous immunoglobulins; MG = myasthenia gravis

All patients in both treatment arms used concomitant medications while on the study. The most commonly used classes of concomitant medications were anticholinesterases (88.8% patients overall; 84.1% in the placebo arm and 93.5%s in the eculizumab arm), corticosteroids (80.0% patients overall; 81.0% in the placebo arm and 79.0% in the eculizumab arm), and proton pump inhibitors (52.8% patients overall; 52.4% in the placebo arm and 53.2% in the eculizumab arm).

Immunosuppressant therapy other than prednisone was used during the study by 82.5% patients in the placebo arm and 88.7% patients in the eculizumab arm. Specific supportive cholinesterase inhibitors and ISTs used by more than 25% of patients overall are presented in Table below.

The total number of concomitant medications taken and the proportion of patients who took at least 1 concomitant medication were similar between treatment groups.

Table 8 Supportive Cholinesterase Inhibitors and Immunosuppressive Therapies Used in >25% of Patients Overall During Study ECU-MG-301 – Safety Set

MG Treatment, n (%)	Placebo (N = 63)	Eculizumab (N = 62)	Total (N = 125)
pyridostigmine bromide	37 (58.7)	38 (61.3)	75 (60.0)
prednisone	26 (41.3)	26 (41.9)	52 (41.6)
azathioprine	21 (33.3)	20 (32.3)	41 (32.8)
mycophenolate mofetil	16 (25.4)	18 (29.0)	34 (27.2)
pyridostigmine	15 (23.8)	18 (29.0)	33 (26.4)

Abbreviations: MG = myasthenia gravis
Source: Study ECU-MG-301 CSR

Measurements of Treatment Compliance

There were no differences between treatment arms in the study drug compliance percentage rate categories, with 56 (88.9%) patients in the placebo arm and 55 (88.7%) patients in the eculizumab arm exhibiting 100% compliance with the study drug. The number of patients who had a dose interruption during the maintenance phase was higher in the placebo arm (8 [12.7%] patients) than the eculizumab arm (2 [3.2%] patients); however, the number of maintenance infusions per patient and the total volume of study drug infused per patient were similar across treatment arms.

- **Numbers analysed**

Of the 63 total patients randomised to the eculizumab arm, 62 (98.4%) were in the FAS, 54 (85.7%) were in the PP Set, and 62 (98.4%) were in the Safety Set.

Of the 63 total patients randomised to the placebo arm, 63 (100.0%) were in the FAS, 56 (88.9%) were in the PP Set, and 63 (100.0%) were in the Safety Set.

Fifteen patients from the FAS were excluded from the PP Set, including 7 patients from the placebo arm and 8 patients from the eculizumab arm

- not having a stable dose of IST therapy at the time of enrolment and/or having a change in IST status during the study (5 patients from the placebo arm and 7 patients from the eculizumab arm).
- MG-ADL assessment performed by himself instead of by a trained evaluator (1 patient from the placebo arm)
- compliance with the study drug was <80% (1 patient from the placebo arm)
- emergent unblinding required during the study (1 patient from the eculizumab arm)

- **Outcomes and estimation**

Myasthenia Gravis Activities of Daily Living Total Score

Primary Efficacy Endpoint: Change from Baseline in MG-ADL total score at Week 26 (Worst-Rank ANCOVA)

The pre-specified primary MG-ADL Worst-Rank ANCOVA for the FAS achieved a p-value of 0.0698. For patients who completed 26 weeks without rescue therapy, the mean (SD) change from Baseline to Week 26 in MG-ADL total score was greater in patients who received eculizumab (-4.7 [4.32]) than in patients who received placebo (-2.8 [3.07]).

Table 9 Change from Baseline in Myasthenia Gravis Activities of Daily Living Total Score at Week 26: ANCOVA Worst-Rank Analysis – Full Analysis Set of Study ECU-MG-301

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Worst-Rank 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	---	---

Note: p-value from Worst-Rank ANCOVA model to test whether treatment arms are equal. The Worst-Rank model includes the following terms: treatment, the pooled MGFA randomization stratification variable, and MG-ADL total score at Baseline. Patients are ranked as indicated in the tabular output with worst ranks based on time to death, time to MG Crisis, time to rescue therapy or dropout, and finally change in MG-ADL at Week 26 or LOCF with greatest improvement getting the rank of 1.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Max = maximum; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGFA = Myasthenia Gravis Foundation of America; Min = minimum

The primary MG-ADL Worst-Rank ANCOVA for the PP Set achieved a p-value of 0.0305.

Sensitivity Analysis

Pre-specified ANCOVA sensitivity analysis is summarized in Table 10 below.

Table 10 Week 26 Analysis of Covariance for Myasthenia Gravis Activities of Daily Living Profile – Full Analysis Set of Study ECU-MG-301

Parameter	Final Analysis	
Change from Baseline	**Placebo (N = 63)**	**Eculizumab (N = 62)**
LS Mean (SEM)	-2.6 (0.48)	-4.0 (0.48)
95% CI for LS mean	(-3.52, -1.63)	(-4.96, -3.04)
Difference in LS Means (95% CI)	-1.4 (-2.77, -0.07)	
p-value[a]	0.0390	

a nominal p-value
Abbreviations: CI = confidence interval; LS = least-squares;

Pre-specified analysis of the change from Baseline at Week 26, based on the Repeated-Measures model is presented in the table 11 below

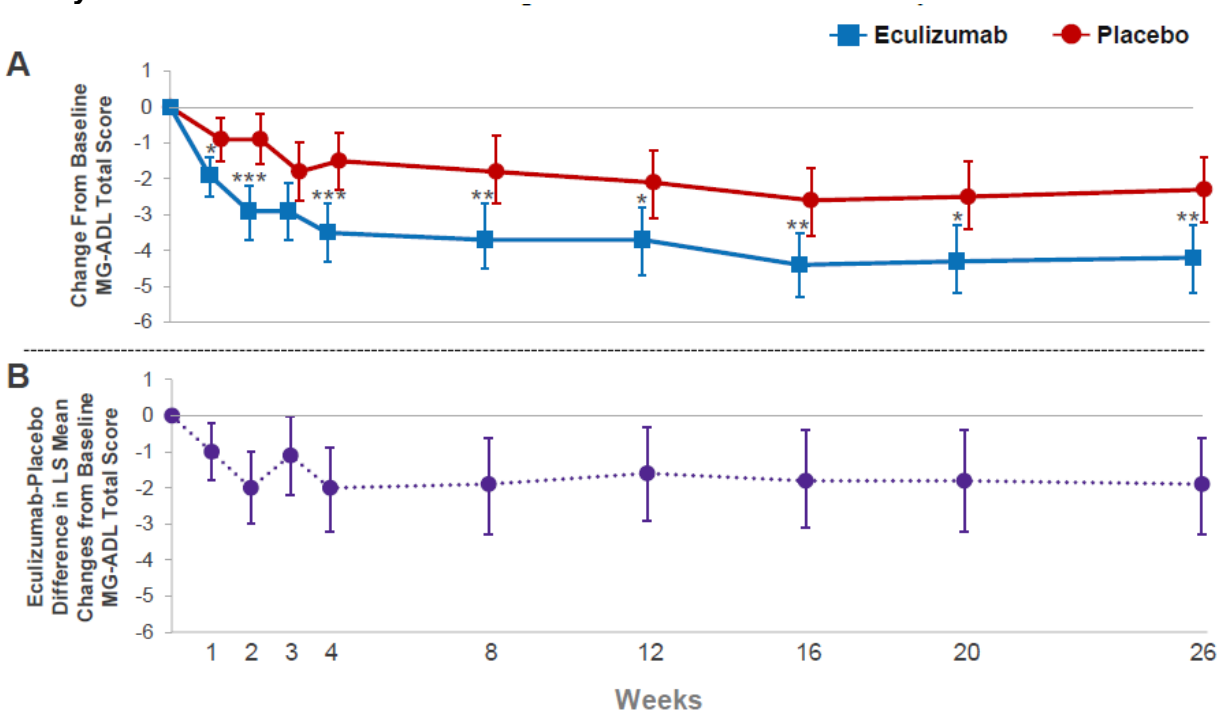
Table 11 Week 26 Repeated-Measures Analysis of Myasthenia Gravis Activities of Daily Living Profile – Full Analysis Set of Study ECU-MG-301

Parameter	Final Analysis	
Change from Baseline	**Placebo (N = 60)**	**Eculizumab (N = 57)**
LS Mean (SEM)	-2.3 (0.48)	-4.2 (0.49)
95% CI for LS mean	(-3.2, -1.4)	(-5.2, -3.3)
Difference in LS Means (95% CI)	-1.9 (-3.3, -0.6)	
p-value[a]	0.0058	

a nominal p-value
Abbreviations: CI = confidence interval; LS = least-squares;

Figure 10 presents the change from Baseline in MG-ADL total score over time (A) and the difference in LS means from the Repeated-Measures analysis (95% CI) (B). This pre-specified analysis shows the rapid onset of the effect of eculizumab as compared with placebo that is evident at Week 1, and the clear difference in response between eculizumab-treated patients and placebo-treated patients through Week 26.

Figure 10 Change from Baseline in Myasthenia Gravis Activities of Daily Living Profile Total Score (LS Mean and 95% CI) and Eculizumab-Placebo Difference in LS Mean (95% CI) over Time from Baseline to Week 26: Repeated Measures – Full Analysis Set of Study ECU-MG-301



*p<0.05, **p<0.01, ***p<0.001 represent the two-sided nominal p-values for the comparison of treatment arms in change from Baseline in the MG-ADL total score by visit using a Repeated-Measures model.
Abbreviations: CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living profile
Source: Study ECU-MG-301 CSR

Secondary Efficacy Endpoints

- Proportion of Patients With at Least a 3-Point Reduction in MG-ADL Total Score

A clinical responder was defined as any patient who demonstrated ≥3-point improvement at Week 26 without using rescue therapy.

There was a significantly larger proportion of clinical responders in the eculizumab arm (37 [59.7%] patients) than in the placebo arm (25 [39.7%] patients) based on a ≥3-point reduction in MG-ADL total score from Baseline to Week 26 with no rescue therapy (p=0.0229). In both treatment arms, more patients in the MGFA Class IIb/IIIb/IVb group had a ≥3-point reduction in MG-ADL total score from Baseline to Week 26 and no rescue therapy than patients in the MGFA Class IIa/IIIa/IVa group.

Table 12 Proportion of Patients with at Least a 3-Point Reduction in Myasthenia Gravis Activities of Daily Living Total Score from Baseline to Week 26 and No Rescue Therapy by Treatment Arm Using CMH Test – Full Analysis Set of Study ECU-MG-301

	Statistic	Placebo (N = 63) n/N (%)	Eculizumab (N = 62) n/N (%)	Difference in % (95% CI)	p-value
Overall	n/N (%)	25/63 (39.7)	37/62 (59.7)	20.0 (2.8, 37.2)	0.0229
	95% CI of %	(27.6, 52.8)	(46.4, 71.9)		

Note: P-value is from a CMH test, testing for a difference in proportions between treatments, adjusting for the pooled MGFA randomization stratification variable.
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; MGFA = Myasthenia Gravis Foundation of America

The proportion of patients experiencing a reduction in MG-ADL total score of ≥3 points through ≥8 points and no rescue therapy had a nominal p-value of <0.05 using the CMH test after adjusting for the pooled MGFA randomization stratification variable for the comparison between treatment arms, favouring eculizumab at all thresholds of point reduction.

Quantitative Myasthenia Gravis Total Score

- *Change from Baseline in QMG total score at Week 26 (Worst-Rank ANCOVA)*

The pre-specified QMG Worst-Rank ANCOVA achieved a p-value of 0.0129. For patients who completed 26 weeks without rescue therapy, the mean (SD) change from Baseline to Week 26 in QMG total score was greater in patients who received eculizumab (-5.4 [4.80]) than in patients who received placebo (-2.4 [3.70]).

Table 13 Worst-Rank Analysis of Covariance for Quantitative Myasthenia Gravis Score for Disease Severity – Full Analysis Set of Study ECU-MG-301

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value[a]
Worst-Rank 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	---	---

Notes: p-value from Worst-Rank ANCOVA model to test whether treatment arms are equal. The Worst-Rank model includes the following terms: treatment, the pooled MGFA randomization stratification variable, and QMG total score at Baseline. Patients are ranked as indicated in the tabular output with worst ranks based on time to death, time to MG Crisis, time to rescue therapy or dropout, and finally change in QMG at Week 26 or LOCF with greatest improvement getting the rank of 1.
a nominal p-value
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; QMG = Quantitative Myasthenia Gravis score for disease severity
Source: Study ECU-MG-301 CSR

Sensitivity Analysis

The change from Baseline in QMG total score at Week 26 using the pre-specified ANCOVA sensitivity analysis is summarized in Table 15. For the FAS, the LS mean (SEM) change from Baseline in QMG total score at Week 26 using the ANCOVA sensitivity analysis was -1.6 (0.59) for the placebo arm and -4.2 (0.60) for the eculizumab arm (p = 0.0032).

Table 14 Week 26 Analysis of Covariance for Quantitative Myasthenia Gravis Score for Disease Severity – Full Analysis Set of Study ECU-MG-301

Parameter	Final Analysis	
Change from Baseline	**Placebo (N = 63)**	**Eculizumab (N = 62)**
LS Mean (SEM)	-1.6 (0.59)	-4.2 (0.60)
95% CI for LS mean	(-2.82, -0.47)	(-5.37, -3.00)
Difference in LS Means (95% CI)	-2.5 (-4.21, -0.87)	
p-value[a]	0.0032	

a nominal p-value
Abbreviations: CI = confidence interval; LS = least squares;

Table 15 below presents an alternative and complementary pre-specified analysis of the change from Baseline at Week 26, based on the Repeated-Measures model.

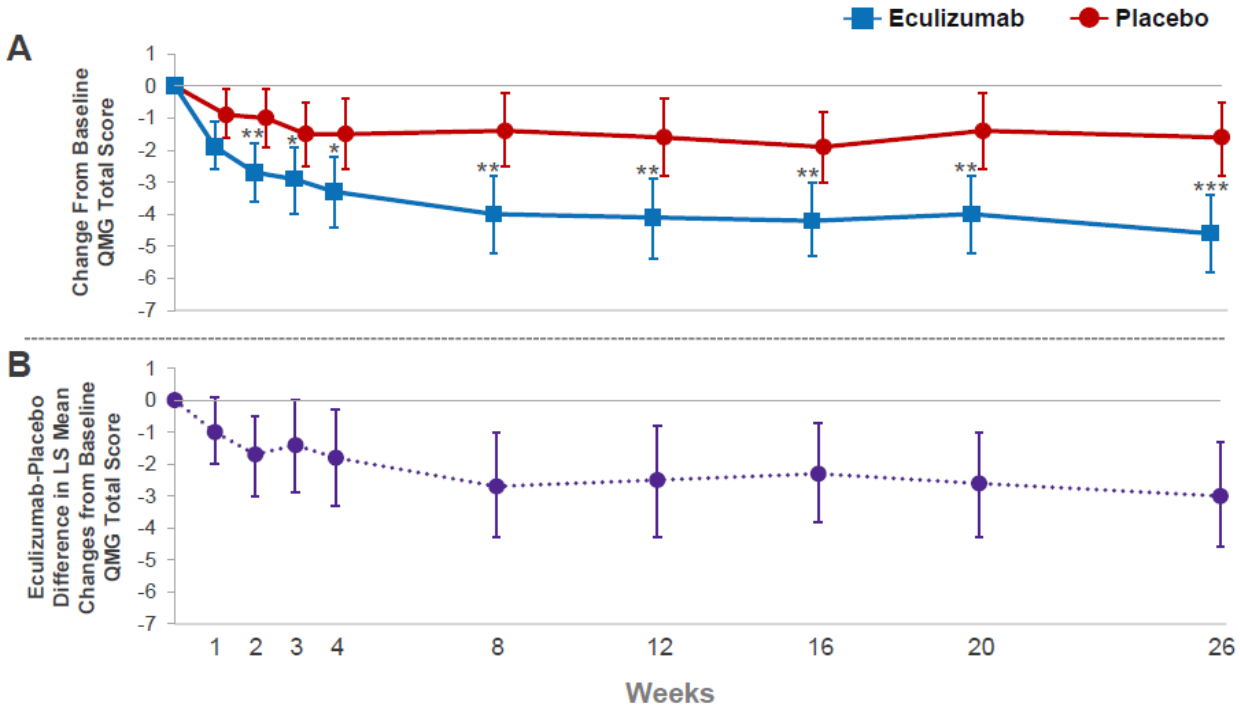
Table 15 Week 26 Repeated-Measures Analysis of Quantitative Myasthenia Gravis Score for Disease Severity – Full Analysis Set of Study ECU-MG-301

Parameter	Final Analysis	
Change from Baseline	**Placebo (N = 60)**	**Eculizumab (N = 56)**
LS Mean (SEM)	-1.6 (0.59)	-4.6 (0.60)
95% CI for LS mean	(-2.8, -0.5)	(-5.8, -3.4)
Difference in LS Means (95% CI)	-3.0 (-4.6, -1.3)	
p-value[a]	0.0006	

a nominal p-value
Abbreviations: CI = confidence interval; LS = least squares;

Figure 11 presents the change from Baseline in QMG total score over time (A) and the difference in LS means from the pre-specified Repeated-Measures analysis (95% CI) (B). As for the MG-ADL, this pre-specified analysis shows the rapid onset of the effect of eculizumab as compared with placebo and the clear difference in response between eculizumab-treated patients and placebo-treated patients through Week 26.

Figure 11 Change from Baseline in Quantitative Myasthenia Gravis Total Score for Disease Severity (Least Squares Mean and 95% CI) and Eculizumab-Placebo Difference in Least Squares Mean (95% CI) over Time from Baseline to Week 26: Repeated Measures – Full Analysis Set of Study ECU-MG-301



*p<0.05, **p<0.01, ***p<0.001 represent the two-sided nominal p-values for the comparison of treatment arms in change from Baseline in the QMG total score by visit using a Repeated-Measures model.
Abbreviations: CI = confidence interval; LS = least squares; QMG = Quantitative Myasthenia Gravis score for disease severity

Proportion of Patients with at Least a 5-Point Reduction in Quantitative Myasthenia Gravis Total Score

A significantly larger proportion of patients in the eculizumab arm (28 [45.2%] patients) than the placebo arm (12 [19.0%] patients) had a ≥5-point reduction in the QMG total score from Baseline to Week 26 and no rescue therapy (p = 0.0018). The difference between treatment arms was similar when comparing patients in each pooled MGFA stratification group. In both treatment arms, more patients in the MGFA Class IIb/IIIb/IVb group had a ≥5-point reduction in the MG-ADL total score from Baseline to Week 26 and no rescue therapy than patients in the MGFA Class IIa/IIIa/IVa group.

Table 16 Proportion of Patients with at Least a 5-Point Reduction in Quantitative Myasthenia Gravis Total Score from Baseline to Week 26 and No Rescue Therapy by Treatment Arm Using Cochran-Mantel-Haenszel Test – Full Analysis Set of Study ECU-MG-301

	Statistic	Placebo (N = 63) n/N (%)	Eculizumab (N = 62) n/N (%)	Difference in % (95% CI)	p-value
Overall	n/N (%)	12/63 (19.0)	28/62 (45.2)	26.2 (10.4, 41.8)	0.0018
	95% CI of %	(10.2, 30.9)	(32.5, 58.3)		

Note: P-value is from a CMH test, testing for a difference in proportions between treatments, adjusting for the pooled MGFA randomization stratification variable.
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; MGFA = Myasthenia Gravis Foundation of America

A post-hoc analysis was performed to assess the number of patients in each treatment arm with both a ≥3-point reduction in MG-ADL total score and a ≥5-point reduction in QMG total score from Baseline at Week 26. Between Baseline and Week 26, 8 (12.7%) patients in the placebo arm and 25 (40.3%) patients in the

eculizumab arm experienced both a ≥3-point reduction in MG-ADL total score and a≥5-point reduction in QMG total score and no rescue therapy.

Myasthenia Gravis Composite Total Score

The pre-specified MGC Worst-Rank ANCOVA achieved a p-value of 0.1026. For patients who completed 26 weeks without rescue therapy, the mean (SD) change from Baseline to Week 26 in MGC total score was greater in patients who received eculizumab (-9.2 [8.08]) than in patients who received placebo (-6.0 [6.19]).

Table 17 Worst-Rank Analysis of Covariance for Myasthenia Gravis Composite Score – Full Analysis Set of Study ECU-MG-301

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value[a]
Worst-Rank 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	---	---

Notes: p-value from Worst-Rank ANCOVA model to test whether treatment arms are equal. The Worst-Rank model includes the following terms: treatment, the pooled MGFA randomization stratification variable, and MGC total score at Baseline. Patients are ranked as indicated in the tabular output with worst ranks based on time to death, time to MG Crisis, time to rescue therapy or dropout, and finally change in MGC at Week 26 or LOCF with greatest improvement getting the rank of 1.
a nominal p-value
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; MG = myasthenia gravis; MGC = Myasthenia Gravis Composite score; MGFA = Myasthenia Gravis Foundation of America;

Sensitivity Analyses

Table 18 below presents the pre-specified standard ANCOVA analysis for the MGC. Greater improvement in the LS mean (SEM) change from Baseline to Week 26 in MGC total score was seen in patients who received eculizumab (-7.8 [0.95]) than in patients who received placebo (-5.0 [0.94]; p=0.0406).

Table 18 Week 26 Analysis of Covariance for Myasthenia Gravis Composite Score – Full Analysis Set of Study ECU-MG-301

Parameter	Final Analysis	
Change from Baseline	Placebo (N = 63)	Eculizumab (N = 62)
LS Mean (SEM)	-5.0 (0.94)	-7.8 (0.95)
95% CI for LS Mean	(-6.90, -3.17)	(-9.70, -5.93)
Difference in LS Means (95% CI)	-2.8 (-5.43, -0.12)	
p-value[a]	0.0406	

a nominal p-value
Abbreviations: CI = confidence interval; LS = least squares

Table 19 presents an alternative and complementary pre-specified analysis of the change from Baseline at Week 26, based on the Repeated-Measures model.

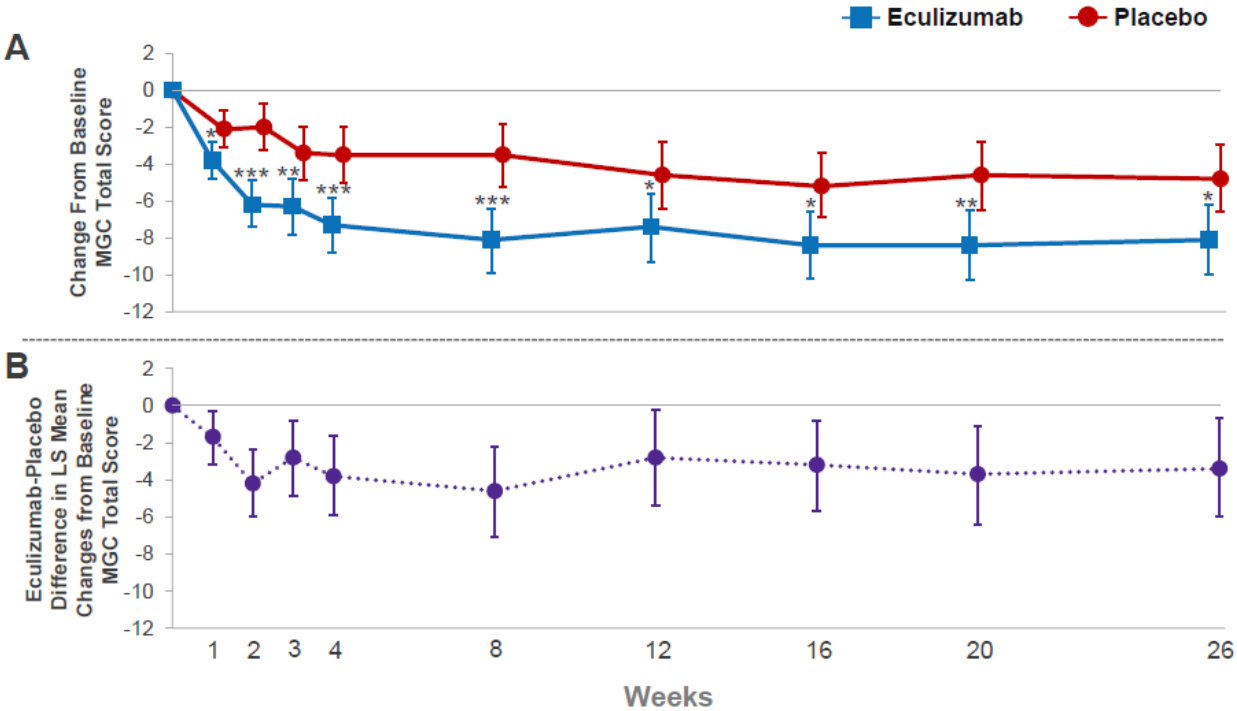
Table 19 Week 26 Repeated-Measures Analysis of Myasthenia Gravis Composite Score – Full Analysis Set of Study ECU-MG-301

Parameter	Final Analysis	
Change from Baseline	**Placebo (N = 60)**	**Eculizumab (N = 57)**
LS Mean (SEM)	-4.8 (0.94)	-8.1 (0.96)
95% CI for LS Mean	(-6.6, -2.9)	(-10.0, -6.2)
Difference in LS Means (95% CI)	-3.4 (-6.0, -0.7)	
p-value[a]	0.0134	

a nominal p-value
Abbreviations: CI = confidence interval; LS = least squares
Source: Study ECU-MG-301 CSR

Figure 12 below presents the change from Baseline in MGC total score over time (A) and the difference in LS means from the Repeated-Measures analysis (95% CI) (B). As was demonstrated for the MG-ADL and QMG, this pre-specified analysis shows the rapid onset of the treatment effect of eculizumab and the clear separation in response between eculizumab-treated patients and placebo-treated patients through 26 weeks.

Figure 12 Change from Baseline in Myasthenia Gravis Composite Score Total Score (LS Mean and 95% CI) and Eculizumab-Placebo Difference in LS Mean (95% CI) over Time from Baseline to Week 26: Repeated Measures–Full Analysis Set of Study ECU-MG-301



*p<0.05, **p<0.01, ***p<0.001 represent the two-sided nominal p-values for the comparison of treatment arms in change from Baseline in the MGC total score by visit using a Repeated-Measures model.
Abbreviations: CI = confidence interval; LS = least squares; MGC = Myasthenia Gravis Composite score

Myasthenia Gravis Quality of Life 15 Total Score

The pre-specified MG-QoL15 Worst-Rank ANCOVA achieved a p-value of 0.0281. For patients who completed 26 weeks without rescue therapy, the mean (SD) change from Baseline to Week 26 in MG-QoL15 total score was greater in patients who received eculizumab (-13.5 [14.07]) than in patients who received placebo (-6.5 [9.40]).

Table 20 Worst-Rank Analysis of Covariance for Myasthenia Gravis Quality of Life 15-item Scale – Full Analysis Set of Study ECU-MG-301

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value[a]
Worst-Rank 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	---	---

Notes: p-value from Worst-Rank ANCOVA model to test whether treatment arms are equal. The Worst-Rank model includes the following terms: treatment, the pooled MGFA randomization stratification variable, and MG-QoL15 total score at Baseline.
Patients are ranked as indicated in the tabular output with worst ranks based on time to death, time to MG Crisis, time to rescue therapy or dropout, and finally change in MG-QoL15 at Week 26 or LOCF with greatest improvement getting the rank of 1.
a nominal p-value
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MG-QoL15 = Myasthenia Gravis Quality of Life 15-item scale

Sensitivity Analyses

The change from Baseline in the MG-QoL15 total score at Week 26 using the pre-specified sensitivity analyses based on ANCOVA and Repeated Measures are summarized in the following tables.

Table 21 Week 26 Analysis of Covariance for Myasthenia Gravis Quality of Life 15-item Scale – Full Analysis Set of Study ECU-MG-301

ANCOVA	Final Analysis	
Change from Baseline	**Placebo (N = 63)**	**Eculizumab (N = 62)**
LS Mean (SEM)	-6.0 (1.49)	-11.3 (1.50)
95% CI for LS mean	-8.99, -3.08	-14.24, -8.28
Difference in LS Means (95% CI)	-5.2 (-9.43, -1.03)	
p-value[a]	0.0152	

a nominal p-value
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares

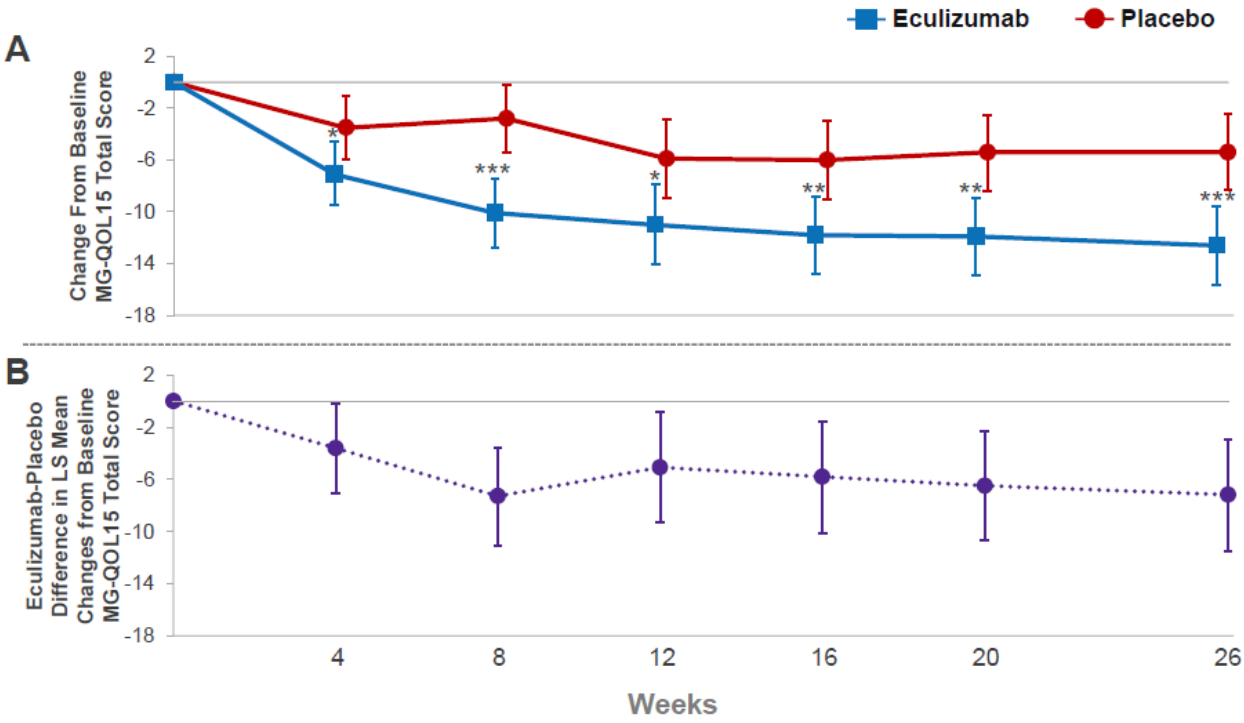
Table 22 Week 26 Repeated-Measures Analysis of Myasthenia Gravis Quality of Life 15-item Scale – Full Analysis Set of Study ECU-MG-301

Parameter	Final Analysis	
Change from Baseline	**Placebo (N = 60)**	**Eculizumab (N = 57)**
LS Mean (SEM)	-5.4 (1.49)	-12.6 (1.52)
95% CI for LS mean	(-8.3, -2.4)	(-15.6, -9.6)
Difference in LS Means (95% CI)	-7.2 (-11.5, -3.0)	
p-value[a]	0.0010	

a nominal p-value
Abbreviations: CI = confidence interval; LS = least squares

Figure 13 below presents the change from Baseline in MG-QoL15 total score over time (A) and the difference in LS means from the pre-specified Repeated-Measures analysis (95% CI) (B). Treatment benefit of eculizumab was observed at the first assessment time point (Week 4) and, similar to the MG-ADL, QMG, and MGC assessments, there was a clear separation in response between eculizumab-treated patients and placebo-treated patients through 26 weeks.

Figure 13 Change from Baseline in Myasthenia Gravis Quality of Life 15-item Scale Total Score (LS Mean and 95% CI) and Eculizumab-Placebo Difference in Least Squares Mean (95% CI) over Time from Baseline to Week 26: Repeated Measures – Full Analysis Set of Study ECU-MG-301



*p<0.05, **p<0.01, ***p<0.001 represent the two-sided nominal p-values for the comparison of arms in change from Baseline in the MG-QoL15 total score by visit using a Repeated-Measures model.
Abbreviations: CI = confidence interval; LS = least squares; MG-QoL15 = Myasthenia Gravis Quality of Life 15-item scale
Source: Study ECU-MG-301 CSR

Tertiary Efficacy Endpoints

- Neuro-QoL Fatigue Total Score: The pre-specified Worst-Rank ANCOVA achieved a p-value of 0.0168. For patients who completed 26 weeks without rescue therapy, the mean (SD) change from Baseline to Week 26 in Neuro-QoL Fatigue total score was greater in patients who received eculizumab (-18.2 [19.60]) than in patients who received placebo (-9.1 [14.58]).
- A significantly greater proportion of patients in the eculizumab arm than the placebo arm experienced improvement in their MGFA PIS from Baseline at Week 4 (p = 0.0006), Week 12 (p = 0.0361), and Week 26 (p = 0.0178) using the CMH test adjusting for the pooled MGFA randomization stratification variable.

Table 23 Change from Baseline in Myasthenia Gravis Foundation of America Post-Intervention Status at Week 26 and Other Study Visits by Treatment Arm (Cochran-Mantel-Haenszel Test Analysis) – Full Analysis Set of Study ECU-MG-301

	Change from Baseline in MGFA Post-Intervention Status						
	Placebo (N = 63)			Eculizumab (N = 62)			
Visit	Improved n/N (%)	Unchanged n/N (%)	Worse n/N (%)	Improved n/N (%)	Unchanged n/N (%)	Worse n/N (%)	p-value
Week 4	15/62 (24.2)	42/62 (67.7)	5/62 (8.1)	32/60 (53.3)	27/60 (45.0)	1/60 (1.7)	0.0006
Week 12	22/61 (36.1)	35/61 (57.4)	4/61 (6.6)	30/56 (53.6)	25/56 (44.6)	1/56 (1.8)	0.0361
Week 26	25/60 (41.7)	30/60 (50.0)	5/60 (8.3)	35/57 (61.4)	21/57 (36.8)	1/57 (1.8)	0.0178

Abbreviations: MGFA = Myasthenia Gravis Foundation of America
Source: Study ECU-MG-301 CSR

- The pre-specified EQ-5D Index Score Worst-Rank ANCOVA achieved a p-value of 0.9815. For patients who completed 26 weeks without rescue therapy, the mean (SD) change from Baseline to Week 26 in EQ-5D Index Score was 0.07 (0.180) in patients who received eculizumab and 0.05 (0.171) in patients who received placebo. Baseline PCB 0.69 (0.184) versus ECU 0.70 (0.133)

Rescue Therapy and Clinical Deterioration

A higher proportion of patients received rescue medication in the placebo arm: 12 of 63 (19.0%) compared with 6 of 62 (9.7%) eculizumab patients. In addition, 15 of the 63 (23.8%) placebo patients reported clinical deterioration (with 11 meeting protocol-defined criteria) compared with 6 of 62 (9.7%) eculizumab patients (6 meeting protocol-defined criteria). One MG crisis occurred in a patient receiving eculizumab.

Table 24 Rescue Therapy and Clinical Deterioration – Full Analysis Set of Study ECU-MG-301

Rescue Therapy	Placebo (N = 63) n (%)	Eculizumab (N = 62) n (%)
Total number of patients requiring rescue therapy	12 (19.0)	6 (9.7)
Total number of patients receiving high dose corticosteroids rescue	5 (7.9)	0 (0.0)
Total number of patients receiving plasmapheresis/plasma exchange rescue	4 (6.3)	3 (4.8)
Total number of patients receiving IVIg rescue	6 (9.5)	4 (6.5)
Total number of patients receiving other rescue therapy rescue	2 (3.2)	1 (1.6)
Total number of clinical deterioration events requiring rescue therapy	24	13
Total number of patients reporting clinical deterioration	15 (23.8)	6 (9.7)
Total number of patients reporting clinical deterioration based on protocol criteria[a]	11 (17.5)	6 (9.7)

Note: Clinical deteriorations and rescues after Week 26 are not represented in the table. Patients may be rescued with 1 or more therapies. Patients may have experienced more than 1 category of clinical deterioration events.
a Protocol-defined MG clinical deterioration a patient experiencing 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 (ie, talking, chewing, swallowing, breathing, upper and lower extremity weakness): To Grade 3, or 2-point worsening; 3. The treating physician believes that the patient's health is in jeopardy if rescue therapy is not given.
Abbreviations: IVIg = intravenous immunoglobulins; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile
Source: Study ECU-MG-301 CSR

Biomarker

Mean AchR antibody titers were reduced relative to Baseline at Weeks 12 and 26 for patients in the placebo arm. Titers were reduced at Week 12 relative to Baseline in the eculizumab arm, but were elevated at Week 26. High variability was observed in the AchR antibody titers across patients in both treatment arms.

Table 25 Summary of Acetylcholine Receptor Antibody Titers and Changes from Baseline by Treatment Arm and Visit – Safety Set of Study ECU-MG-301

		Placebo (N = 63)			Eculizumab (N = 62)		
Visit	Statistic	Baseline	Visit	Change from Baseline	Baseline	Visit	Change from Baseline
Screening (Baseline)	n	63			62		
	Mean (SD), nmol/L	121.475 (199.5881)			94.343 (172.3732)		
	Median	28.000			11.370		
	Min, Max	0.64, 770.61			0, 892		
Week 12	n	59	59	59	58	58	58
	Mean (SD), nmol/L	105.070 (176.9255)	84.996 (152.9721)	-20.074 (143.0121)	100.387 (176.6927)	91.841 (178.8532)	-8.546 (77.3083)
	Median	16.120	19.100	-0.330	14.945	10.090	-0.185
	Min, Max	0.64, 770.61	0.54, 735.74	-629.84, 450.81	0, 892	0.5, 882.56	-280, 259.6
Week 26	n	58	58	58	56	56	56
	Mean (SD), nmol/L	118.121 (190.7716)	103.000 (189.5001)	-15.121 (143.2923)	98.107 (176.7016)	124.771 (269.8923)	26.664 (147.5221)
	Median	28.105	24.315	-0.965	14.945	9.270	-0.065
	Min, Max	0.64, 770.61	0.48, 999	-670.62, 354	0.52, 892	0.45, 1281	-283, 721.77

Abbreviations: Max = maximum; Min = minimum

- **Subgroup Analysis**

The MG-ADL total score between Baseline and Week 26 showed a trend toward greater reduction in the eculizumab arm than the placebo arm in patients aged 18 to 65 years than in patients aged >65 years, and in females than in males. Small sample sizes of some race and region subgroups limit interpretation of these subgroup analyses.

Patients in both the placebo and eculizumab arms showed a trend toward increased improvement in MG-ADL total score in patients with a higher Baseline MG-ADL total score; all Baseline MG-ADL subgroups showed a greater improvement from Baseline in the eculizumab arm than the placebo arm at Week 26.

The difference between treatment arms in the change from Baseline in MG-ADL total score at Week 26 was similar in patients who enrolled into the study post-thymectomy and those without prior thymectomy.

Subgroup analyses of QMG total score were in concordance with those for MG-ADL total score.

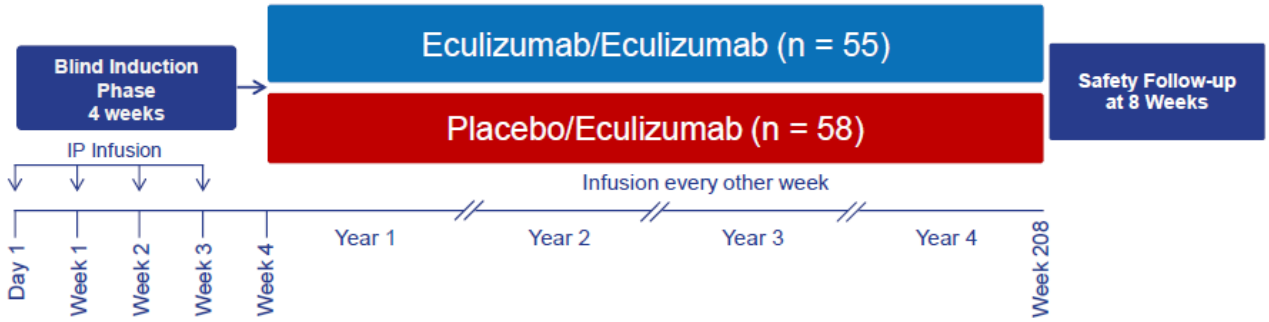
2.4.2.2. Study ECU-MG-302

At the time of the submission, the Phase 3, open-label, long-term extension study was on-going. Patients who completed Study ECU-MG-301 were eligible for entry into this extension study. Of the 125 patients enrolled in Study ECU-MG-301, 117 continued into Study ECU-MG-302.

The first interim clinical study report included in the submission provided results for the primary, secondary, and tertiary efficacy endpoints as defined in the protocol for the Extension FAS as of the 01 Mar 2016 clinical database cut-off date.

To preserve the blinded nature of Study ECU-MG-301, all patients underwent a Blind Induction Phase prior to entering the Open-Label Maintenance Phase of Study ECU-MG-302. Study drug (eculizumab, placebo, or eculizumab plus placebo) was administered weekly during the induction phase.

Table 26 Study Design ECU-MG-302



Abbreviations: IP = investigational product

The evaluation of the long-term safety of eculizumab in refractory gMG patients was the primary objective of Study ECU-MG-302; demonstrating long-term maintenance of efficacy was the secondary objective.

The schedule of assessments in the first 26 weeks of Study ECU-MG-302 was identical to that in the 26-week Study Period of Study ECU-MG-301 for the primary (MG-ADL) and all secondary (QMG, MGC, and MG-QoL15) efficacy endpoint assessments. After the first 26 weeks in ECU-MG-302, efficacy assessments were performed less frequently, occurring every 3 months to Year 1 and then every 6 months thereafter to lessen the burden of clinical assessments on each patient, while continuing to collect long-term efficacy and safety results.

Statistical methods:

Extension Full Analysis Set:

Efficacy analyses in this interim clinical study report (CSR) were performed using the Extension FAS. The Extension FAS consists of all patients who received at least 1 dose of eculizumab in Study ECU-MG-302 and had at least 1 post-study drug infusion efficacy assessment.

Extension Safety Set:

Safety analyses in this interim CSR were performed using the Extension Safety Set, which consists of patients who received at least 1 dose of eculizumab in Study ECU-MG-302.

Treatment Arms:

Analyses are performed by treatment arms (ie, placebo/eculizumab and eculizumab/eculizumab where the designation before '/' denotes the blinded study treatment the patient had received in Study ECU-MG-301). As all patients received eculizumab in Study ECU-MG-302, the designation following '/' is eculizumab for all patients in the respective dataset.

Efficacy

Two Baselines were used for efficacy analyses:

1. ECU-MG-302 Baseline, defined as the Day 1 assessment in Study ECU-MG-302 (if the Day 1 assessment was missing, the last previous assessment from Study ECU-MG-301 was used as the Baseline); and,

2. ECU-MG-301 Baseline, defined as Baseline used in the ECU-MG-301 efficacy analyses (Day 1 visit; if Day 1 visit was missing, the Screening Visit was used as Baseline in Study ECU-MG-301).

Primary Efficacy Endpoint:

The primary efficacy endpoint is the change from Baseline in the MG-ADL total score. For both the placebo/eculizumab and eculizumab/eculizumab treatment arms, summaries are presented by treatment arm for MG-ADL total score and change from ECU-MG-302 Baseline at each visit in Study ECU-MG-302. Summaries are also provided for both treatment arms for change from ECU-MG-301 Baseline in MG-ADL total score at each visit in Study ECU-MG-302. The change from ECU-MG-302 Baseline allows for an assessment of treatment effect of eculizumab beyond any placebo effect experienced during Study ECU-MG-301. The change from ECU-MG-301 Baseline allows for an assessment of overall treatment effect and maintenance of treatment effect with continued exposure to eculizumab.

The analyses for the change from ECU-MG-302 Baseline in MG-ADL total score at a particular visit are based on Repeated-Measures models with effects for ECU-MG-302 Baseline MG-ADL total score and visit. Since the eculizumab/eculizumab patients already received 26 weeks of treatment with eculizumab in Study ECU-MG-301, separate Repeated-Measures models are used for each treatment arm. The LS means of change from ECU-MG-302 Baseline in MG-ADL total score and 95% CIs are presented by treatment arm and study visit. P-values assessing whether the LS means equal 0 are presented by treatment arm and study visit. Graphical displays (LS means and 95% CIs) over time are produced by treatment arm and visit. Missing primary endpoint assessments are not imputed.

Analyses focus on study visits through Week 26 of eculizumab treatment in Study ECU-MG-302 by treatment arm. For patients who were treated for at least 26 weeks in Study ECU-MG-302, summaries are provided for MG-ADL total score and change from Baseline at each visit.

Secondary Efficacy Endpoints:

The changes from Baseline in QMG, MGC, and MG-QoL15 total scores are summarized and presented in a similar way as described above for the primary efficacy endpoint. Likewise, a similar approach as that for the primary analysis was taken, which utilized separate Repeated-Measures models with effects for particular Baseline covariates and visit for each treatment arm. The LS means, 95% CIs, and p-values are presented by treatment arm and visit. Graphical displays (LS means and 95% CIs) over time are produced by treatment arm and visit. Missing secondary endpoint assessments are not imputed.

For responder analyses, the proportions of patients with a ≥3-point reduction in the MG-ADL total score or those with a ≥5-point reduction in the QMG total score, from ECU-MG-302 Baseline with no rescue therapy prior to the given visit, are summarized at each visit for the placebo/eculizumab treatment arm. Exact (Clopper-Pearson) 95% CIs for the true proportions are presented.

2.4.2.2.1. Results from *Study ECU-MG-302*

A second interim analysis of Study ECU-MG-302 was performed with a clinical database cut-off date of 21 Sep 2016.

As of the clinical database cut-off on 21 Sep 2016, a total of 117 patients had enrolled and received at least 1 dose of study drug as part of Study ECU-MG-302. One patient was excluded from efficacy analyses for this interim analysis; however, this patient is included in the Safety Population. Therefore, 116 total patients are included in the efficacy analyses and 117 patients are included in the safety analyses for this second interim analysis.

Table 27 Patient Disposition: Enrolled, Treated, Completed, and Discontinued –All Enrolled Patients Set of Study ECU-MG-302

Status	Placebo/Eculizumab n (%)	Eculizumab/Eculizumab n (%)	Total n (%)
Enrolled[a]	61 (100.0)	56 (100.0)	117 (100.0)
Treated (Extension Safety Population)	61 (100.0)	56 (100.0)	117 (100.0)
Discontinued	6 (9.8)	7 (12.5)	13 (11.1)
Adverse event	1 (1.6)	1 (1.8)	2 (1.7)
Death	0 (0.0)	1 (1.8)	1 (0.9)
Physician decision	0 (0.0)	1 (1.8)	1 (0.9)
Withdrawal by patient	5 (8.2)	3 (5.4)	8 (6.8)
Other	0 (0.0)	1 (1.8)	1 (0.9)

Note: A total of 117 patients were treated in the extension study as of 21 Sep 2016.

The eculizumab/eculizumab arm consists of 56 patients, all of whom are in the Extension FAS. The placebo/eculizumab arm consists of 61 patients, of whom 60 (98.4%) are in the Extension FAS.

All patients had been treated with eculizumab as part of Study ECU-MG-302 for at least 26 weeks unless they had discontinued from the study prior to the Week 26 visit. Twenty patients from each treatment arm had been treated with eculizumab as part of Study ECU-MG-302 for at least 52 weeks. Data are reported in this clinical study report out to 52 weeks; however, due to the smaller sample size at Week 52, conclusions are based primarily on the Week 26 data.

Demographic and Other Baseline Characteristics

Table 28 Demographics and Baseline Characteristics by Treatment Arm –Extension Safety Set of Study ECU-MG-302

Variable	Statistic	Placebo/Eculizumab (N = 61)	Eculizumab/Eculizumab (N = 56)	Total (N = 117)
Age at Day 1 (first dose date) in Study ECU-MG-302 (years)	n	61	56	117
	Mean (SD)	47.5 (17.85)	47.2 (15.52)	47.4 (16.70)
	Median	48.0	44.5	45.0
	Min, Max	19, 80	20, 75	19, 80
Sex				
Male	n (%)	20 (32.8)	18 (32.1)	38 (32.5)
Female	n (%)	41 (67.2)	38 (67.9)	79 (67.5)
Ethnicity				
Hispanic or Latino	n (%)	10 (16.4)	8 (14.3)	18 (15.4)
Not Hispanic or Latino	n (%)	48 (78.7)	45 (80.4)	93 (79.5)
Not reported	n (%)	0 (0.0)	2 (3.6)	2 (1.7)
Unknown	n (%)	3 (4.9)	1 (1.8)	4 (3.4)
Race				
Asian	n (%)	16 (26.2)	3 (5.4)	19 (16.2)
Black or African American	n (%)	2 (3.3)	0 (0.0)	2 (1.7)
White	n (%)	41 (67.2)	47 (83.9)	88 (75.2)
Multiple	n (%)	0 (0.0)	1 (1.8)	1 (0.9)
Unknown	n (%)	0 (0.0)	1 (1.8)	1 (0.9)
Other	n (%)	2 (3.3)	4 (7.1)	6 (5.1)
Is the patient of Japanese descent?				
Yes	n (%)	9 (14.8)	3 (5.4)	12 (10.3)
No	n (%)	52 (85.2)	53 (94.6)	105 (89.7)

Abbreviations: Max = maximum; Min = minimum

During Study ECU-MG-302, patients were permitted to change their concomitant IST usage at the discretion of the Investigator. At Baseline, 89 (76.1%) patients were taking prednisone and 98 (83.8%) patients were taking ≥ 1 IST other than prednisone. 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 29 below).

• 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.

Table 29 Summary of Changes in Immunosuppressant Therapy Status – Extension Safety Set of Study ECU-MG-302

Parameter	Placebo/Eculizumab (N = 61)		Eculizumab/Eculizumab (N = 56)		All Patients (N = 117)	
	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

Neisseria meningitidis revaccinations were anticipated in 7 patients during the study as assessed by the Investigator on Day 1; all 7 patients received revaccination.

As of 21 Sep 2016, 106 (90.6%) patients were 100% compliant with treatment during Study ECU-MG-302. Fifteen patients (12.8%) overall had a dose interruption during the study. Three (2.6%) patients had a dose interrupted during the Blind Induction Phase and 13 (11.1%) patients had a dose interrupted during the Maintenance Phase of the study; 1 patient had at least 1 dose interruption during each of the Blind Induction and Maintenance Phases. In 3 of the 15 patients who experienced a dose interruption, the dose interruption was due to an AE; however, in all 15 of these patients, the full intended dose of the study drug was administered.

Efficacy Results

Myasthenia Gravis Activities of Daily Living Total Score

Primary Efficacy Endpoint: Changes from Baseline in the MG-ADL total score

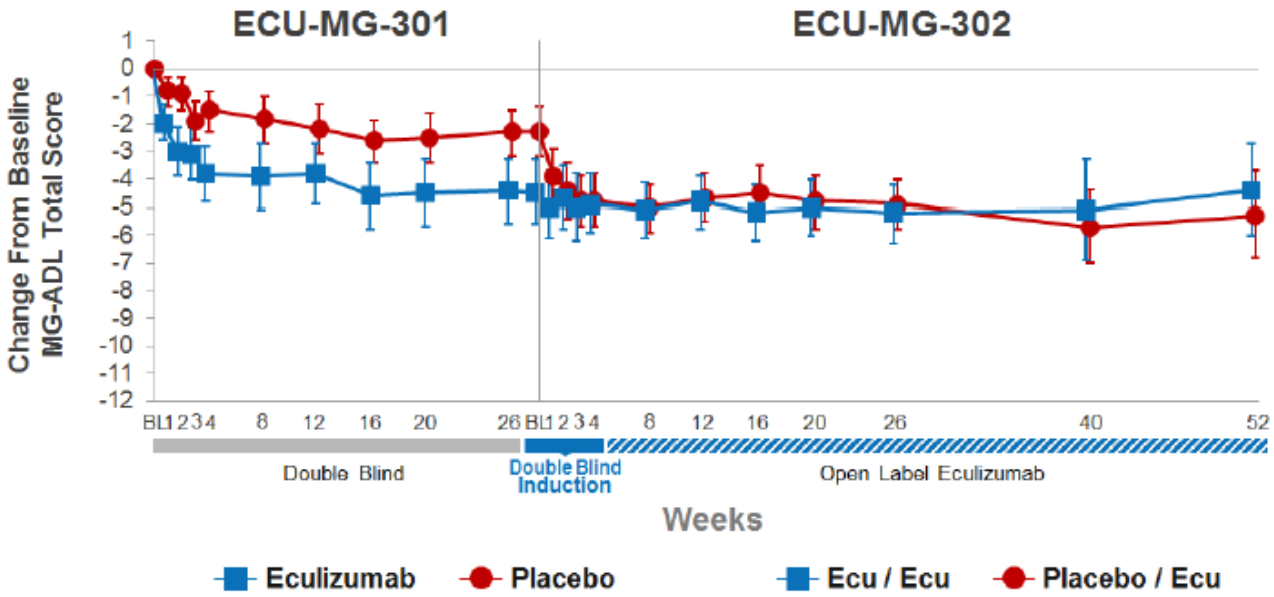
- Change from ECU-MG-302 Baseline: In the eculizumab/eculizumab arm, the MG-ADL total score was unchanged from ECU-MG-302 Baseline at each assessment through Week 52, indicating that the magnitude of treatment effect observed in Study ECU-MG-301 was sustained with continued exposure to eculizumab. In the placebo/eculizumab arm, a change from ECU-MG-302 Baseline in MG-ADL total score was 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).

- Change from ECU-MG-301 Baseline: The treatment effect observed during Study ECU-MG-301 in patients treated with eculizumab during that study (Week 26 mean [95% CI] change from

ECU-MG-301 Baseline: -4.1 [-5.6, -3.3]) was sustained in Study ECU-MG-302 (eculizumab/eculizumab arm), with a mean (95% CI) change in MG-ADL total score from ECU-MG-301 Baseline at Weeks 1, 8, 26 and 52 of Study ECU-MG-302 of -5.0 (-6.1, -3.9), -5.1 (-6.1, -4.1), -5.2 (-6.3, -4.2)and -4.4 (-6.0, -2.7), respectively.

In the placebo/eculizumab arm, a change (mean [95% CI]) from ECU-MG-301 Baseline in MG-ADL total score was observed as early as Week 1 (-3.6 [-4.7, -2.5]) of Study ECU-MG-302. The majority of the overall treatment effect was achieved by Week 3 (-4.3 [-5.3, -3.2]) during the Blind Induction Phase, and was sustained through Week 26 (-4.9 [-6.3, -3.4]).

Figure 14 Change from Baseline in Myasthenia Gravis Activities of Daily Living Profile Total Score (Mean and 95% CI) by Treatment Arm over Time from ECU-MG-301 Baseline to Week 52 in Study ECU-MG-302 – Extension Full Analysis Set



Note: 95% CI is based on t-distribution for each treatment arm at each visit.
Abbreviations: BL = Baseline; CI = confidence interval; Ecu = eculizumab; MG-ADL = Myasthenia Gravis Activities of Daily Living profile

Seventy-five percent of the patients receiving placebo in the prior Study ECU-MG-301 responded to eculizumab in Study ECU-MG-302, with a ≥3-point improvement from ECU-MG-301 Baseline in MG-ADL total score at Week 26 without rescue therapy. This responder rate is comparable to that observed at Week 26 of Study ECU-MG-301 in eculizumab-treated patients (60.0%) and is twice that observed at Week 26 of Study ECU-MG-301 in placebo-treated patients (37.5%).

Table 30 Proportion of Patients with at Least a 3-Point Reduction in Myasthenia Gravis Activities of Daily Living Profile Total Score from ECU-MG-301 Baseline and No Rescue Therapy by Treatment Arm and Visit – Extension Full Analysis Set

Visit	Placebo/Eculizumab (N = 60)		Eculizumab/Eculizumab (N = 56)	
	n/N (%)	95% CI for %[a]	n/N (%)	95% CI for %[a]
ECU-MG-301 Week 1	13/59 (22.0)	(12.3, 34.7)	22/56 (39.3)	(26.5, 53.2)
ECU-MG-301 Week 2	13/60 (21.7)	(12.1, 34.2)	26/56 (46.4)	(33.0, 60.3)
ECU-MG-301 Week 3	25/60 (41.7)	(29.1, 55.1)	28/56 (50.0)	(36.3, 63.7)
ECU-MG-301 Week 4	21/60 (35.0)	(23.1, 48.4)	30/56 (53.6)	(39.7, 67.0)
ECU-MG-301 Week 8	21/60 (35.0)	(23.1, 48.4)	31/55 (56.4)	(42.3, 69.7)
ECU-MG-301 Week 12	25/60 (41.7)	(29.1, 55.1)	31/55 (56.4)	(42.3, 69.7)
ECU-MG-301 Week 16	25/59 (42.4)	(29.6, 55.9)	35/56 (62.5)	(48.5, 75.1)
ECU-MG-301 Week 20	25/60 (41.7)	(29.1, 55.1)	33/56 (58.9)	(45.0, 71.9)
ECU-MG-301 Week 26	24/59 (40.7)	(28.1, 54.3)	33/56 (58.9)	(45.0, 71.9)
ECU-MG-302 Day 1	30/60 (50.0)	(36.8, 63.2)	33/56 (58.9)	(45.0, 71.9)
ECU-MG-302 Week 1	39/60 (65.0)	(51.6, 76.9)	34/55 (61.8)	(47.7, 74.6)
ECU-MG-302 Week 2	44/60 (73.3)	(60.3, 83.9)	31/54 (57.4)	(43.2, 70.8)
ECU-MG-302 Week 3	44/60 (73.3)	(60.3, 83.9)	33/53 (62.3)	(47.9, 75.2)
ECU-MG-302 Week 4	48/60 (80.0)	(67.7, 89.2)	32/55 (58.2)	(44.1, 71.3)
ECU-MG-302 Week 8	46/58 (79.3)	(66.6, 88.8)	39/55 (70.9)	(57.1, 82.4)
ECU-MG-302 Week 12	42/60 (70.0)	(56.8, 81.2)	33/53 (62.3)	(47.9, 75.2)
ECU-MG-302 Week 16	40/57 (70.2)	(56.6, 81.6)	35/53 (66.0)	(51.7, 78.5)
ECU-MG-302 Week 20	40/57 (70.2)	(56.6, 81.6)	34/52 (65.4)	(50.9, 78.0)
ECU-MG-302 Week 26	38/55 (69.1)	(55.2, 80.9)	32/49 (65.3)	(50.4, 78.3)

Note: The ECU-MG-301 Baseline is defined as the last available assessment prior to first dose of study drug in Study ECU-MG-301.
Abbreviations: CI = confidence interval

Secondary Efficacy Endpoints

Quantitative Myasthenia Gravis Total Score

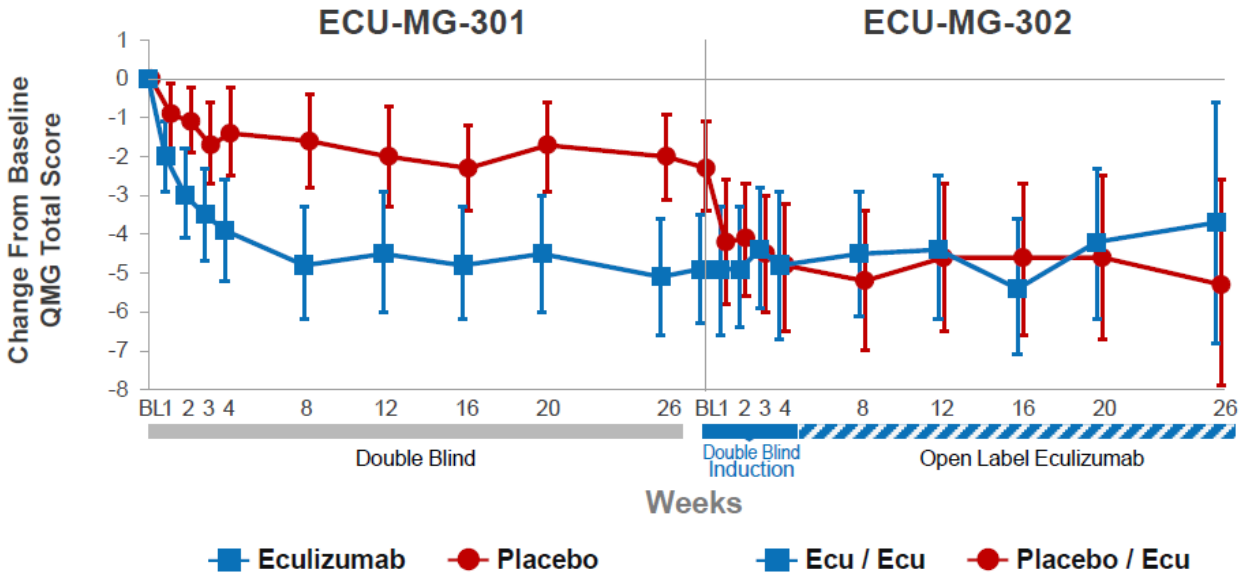
- Change from ECU-MG-302 Baseline: In the eculizumab/eculizumab arm, the QMG total score was essentially unchanged from ECU-MG-302 Baseline at each assessment through Week 26, indicating that the magnitude of treatment effect observed in Study ECU-MG-301 was sustained with continued exposure to eculizumab.

  In the placebo/eculizumab arm, a change from ECU-MG-302 Baseline in QMG total score was observed as early as Week 1 (-1.8 [-2.96, -0.70]; p = 0.0019). The majority of the overall treatment effect was achieved by Week 4 (-3.0 [-4.18, -1.85]; p<0.0001) during the Blind Induction Phase, and was sustained through Week 26 (-3.1 [-4.42, -1.71]; p<0.0001).

- Change from ECU-MG-301 Baseline: The treatment effect observed during Study ECU-MG-301 in patients treated with eculizumab during that study (Week 26 mean [95% CI] change from ECU-MG-301 Baseline: -5.1 [-6.6, -3.6]) was sustained in Study ECU-MG-302 (eculizumab/eculizumab arm), with a mean (95% CI) change in QMG total score from ECU-MG-301 Baseline at Weeks 1, 8, and 26 of Study ECU-MG-302 of -4.9 (-6.6, -3.3), -4.5 (-6.1, -2.9), and -3.7 (-6.8, -0.6), respectively.

  In the placebo/eculizumab arm, a change (mean [95% CI]) from ECU-MG-301 Baseline in QMG total score was observed as early as Week 1 (-4.2 [-5.8, -2.6]) of Study ECU-MG-302. The majority of the overall treatment effect was achieved by Week 4 (-4.8 [-6.5, -3.2]) during the Blind Induction Phase, and was sustained through Week 26 (-5.3 [-7.9, -2.6]).

Figure 15 Change from Baseline in Quantitative Myasthenia Gravis Total Score for Disease Severity (Mean and 95% CI) by Treatment Arm over Time from ECU-MG-301 Baseline to Week 26 in Study ECU-MG-302 – Extension Full Analysis Set



Note: 95% CI is based on t-distribution for each treatment arm at each visit. Abbreviations: BL = Baseline; CI = confidence interval; Ecu = eculizumab; QMG = Quantitative Myasthenia Gravis score for disease severity

At Week 26 of Study ECU-MG-301, 25 (51%) patients treated with eculizumab (of those who continued into Study ECU-MG-302) had attained a ≥5-point improvement in QMG total score and no rescue therapy. This responder rate was maintained at Week 26 of Study ECU-MG-302, at which time 7 of 16 (43.8%) patients had attained a ≥5-point improvement in QMG total score since ECU-MG-302 Baseline and no rescue therapy, demonstrating the durability of treatment effect.

At Week 26 of Study ECU-MG-301, 10 (20.8%) patients treated with placebo (of those who continued into Study ECU-MG-302) had attained a ≥5-point improvement in QMG total score and no rescue therapy. When these patients enrolled in Study ECU-MG-302 and began receiving treatment with eculizumab, an incremental increase in responder rate was observed. At Week 4 of Study ECU-MG-302, 22 of 42 (52.4%) placebo/eculizumab patients obtained a ≥5-point improvement in QMG total score with no rescue therapy. This treatment effect was sustained over 26 weeks of treatment with eculizumab (10 of 20 [50.0%]).

Table 31 Proportion of Patients with at Least a 5-Point Reduction in Quantitative Myasthenia Gravis Total Score for Disease Severity from ECU-MG-301 Baseline and No Rescue Therapy by Treatment Arm and Visit – Extension Full Analysis Set

Visit	Placebo/Eculizumab (N = 60)		Eculizumab/Eculizumab (N = 56)	
	n/N (%)	95% CI for %[a]	n/N (%)	95% CI for %[a]
ECU-MG-301 Week 1	8/59 (13.6)	(6.0, 25.0)	9/55 (16.4)	(7.8, 28.8)
ECU-MG-301 Week 2	7/59 (11.9)	(4.9, 22.9)	17/56 (30.4)	(18.8, 44.1)
ECU-MG-301 Week 3	11/60 (18.3)	(9.5, 30.4)	20/56 (35.7)	(23.4, 49.6)
ECU-MG-301 Week 4	11/59 (18.6)	(9.7, 30.9)	18/56 (32.1)	(20.3, 46.0)
ECU-MG-301 Week 8	11/59 (18.6)	(9.7, 30.9)	25/55 (45.5)	(32.0, 59.4)
ECU-MG-301 Week 12	13/59 (22.0)	(12.3, 34.7)	21/55 (38.2)	(25.4, 52.3)
ECU-MG-301 Week 16	12/59 (20.3)	(11.0, 32.8)	24/56 (42.9)	(29.7, 56.8)
ECU-MG-301 Week 20	12/59 (20.3)	(11.0, 32.8)	26/56 (46.4)	(33.0, 60.3)
ECU-MG-301 Week 26	12/59 (20.3)	(11.0, 32.8)	28/55 (50.9)	(37.1, 64.6)
ECU-MG-302 Day 1	16/60 (26.7)	(16.1, 39.7)	26/55 (47.3)	(33.7, 61.2)
ECU-MG-302 Week 1	25/60 (41.7)	(29.1, 55.1)	26/55 (47.3)	(33.7, 61.2)
ECU-MG-302 Week 2	25/59 (42.4)	(29.6, 55.9)	26/53 (49.1)	(35.1, 63.2)
ECU-MG-302 Week 3	28/58 (48.3)	(35.0, 61.8)	23/53 (43.4)	(29.8, 57.7)
ECU-MG-302 Week 4	32/59 (54.2)	(40.8, 67.3)	26/54 (48.1)	(34.3, 62.2)
ECU-MG-302 Week 8	27/57 (47.4)	(34.0, 61.0)	31/55 (56.4)	(42.3, 69.7)
ECU-MG-302 Week 12	27/60 (45.0)	(32.1, 58.4)	23/52 (44.2)	(30.5, 58.7)
ECU-MG-302 Week 16	31/57 (54.4)	(40.7, 67.6)	22/52 (42.3)	(28.7, 56.8)
ECU-MG-302 Week 20	28/57 (49.1)	(35.6, 62.7)	25/52 (48.1)	(34.0, 62.4)
ECU-MG-302 Week 26	26/55 (47.3)	(33.7, 61.2)	21/48 (43.8)	(29.5, 58.8)

Note: The ECU-MG-301 Baseline is defined as the last available assessment prior to first dose of study drug in Study ECU-MG-301.
Abbreviations: CI = confidence interval

Myasthenia Gravis Composite Total Score

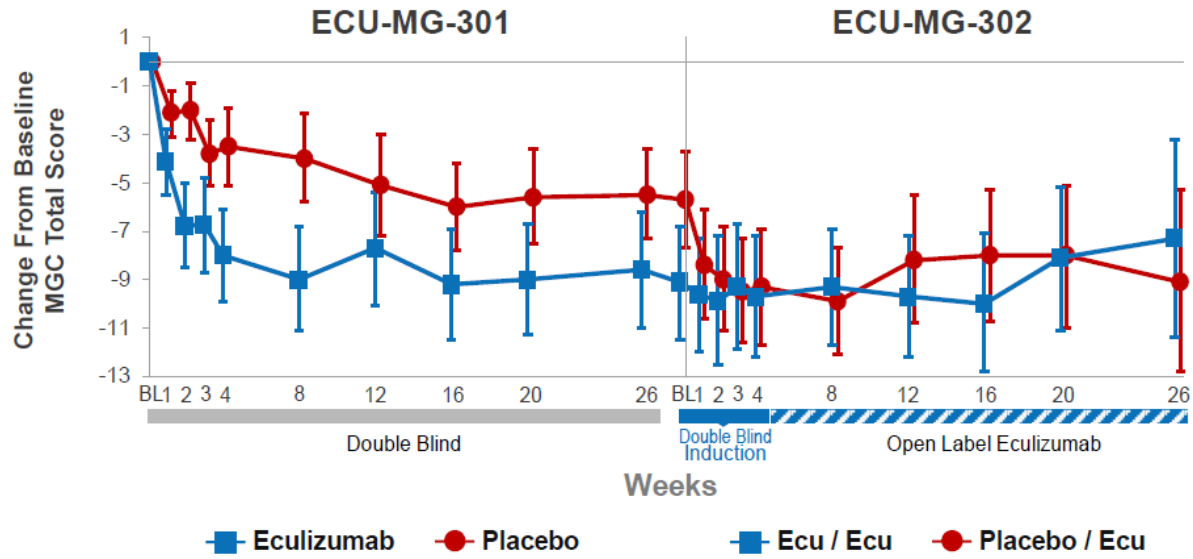
- Change from ECU-MG-302 Baseline: In the eculizumab/eculizumab arm, the MGC total score was essentially unchanged from ECU-MG-302 Baseline at each assessment through Week 26, indicating that the magnitude of treatment effect observed in Study ECU-MG-301 was sustained with continued exposure to eculizumab.

  In the placebo/eculizumab arm, a change from ECU-MG-302 Baseline in MGC total score was observed as early as Week 1 (-2.6 [-4.08, -1.05]; p = 0.0011). The majority of the overall treatment effect was achieved by Week 3 (-4.4 [-5.90, -2.81]; p<0.0001) during the Blind Induction Phase, and was sustained through Week 26 (-4.7 [-6.50, -2.80]; p<0.0001).

- Change from ECU-MG-301 Baseline: The treatment effect observed during Study ECU-MG-301 in patients treated with eculizumab during that study (Week 26 mean [95% CI] change from ECU-MG-301 Baseline: -8.6 [-11.0, -6.2]) was sustained in Study ECU-MG-302 (eculizumab/eculizumab arm), with a mean (95% CI) change in MGC total score from ECU-MG-301 Baseline at Weeks 1, 8, and 26 of Study ECU-MG-302 of -9.6 (-12.0, -7.3), -9.3 (-11.7, -6.9), and -7.3 (-11.4, -3.2), respectively.

  In the placebo/eculizumab arm, a change (mean [95% CI]) from ECU-MG-301 Baseline in MGC total score was observed as early as Week 1 (-8.4 [-10.6, -6.1]) of Study ECU-MG-302. The majority of the overall treatment effect was achieved by Week 3 (-9.5 [-11.6, -7.3]) during the Blind Induction phase, and was sustained through Week 26 (-9.1 [-12.8, -5.3]).

Figure 16 Change from Baseline in Myasthenia Gravis Composite Total Score (Mean and 95% CI) by Treatment Arm over Time from ECU-MG-301 Baseline to Week 26 in Study ECU-MG-302 – Extension Full Analysis Set



Note: 95% CI is based on t-distribution for each treatment arm at each visit.
Abbreviations: BL = Baseline; CI = confidence interval; Ecu = eculizumab; MGC = Myasthenia Gravis Composite score

Myasthenia Gravis Quality of Life 15 Total Score

- Change from ECU-MG-302 Baseline: In the eculizumab/eculizumab arm, the MG-QoL15 total score was essentially unchanged from ECU-MG-302 Baseline at each assessment through Week 26, indicating that the magnitude of treatment effect observed in Study ECU-MG-301 was sustained with continued exposure to eculizumab.

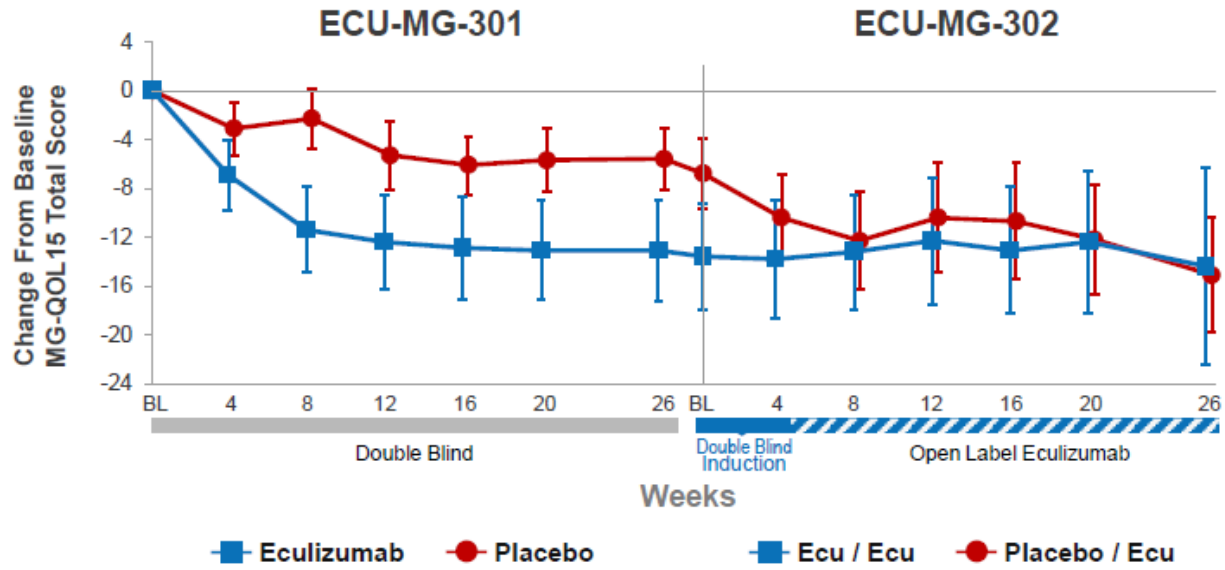
  In the placebo/eculizumab arm, a change from ECU-MG-302 Baseline in MG-QoL15 total score was observed at the first follow-up assessment at Week 4 (-3.9 [-6.40, -1.34]; p = 0.0031). The majority of the overall treatment effect was achieved by Week 4 during the Blind Induction Phase, and was sustained through Week 26 (-5.1 [-8.24, -2.05]; p = 0.0013).

- Change from ECU-MG-301 Baseline: The treatment effect observed during Study ECU-MG-301 in patients treated with eculizumab during that study (Week 26 mean [95% CI] change from ECU-MG-301 Baseline: -13.1 [-17.2, -9.0]) was sustained in Study ECU-MG-302 (eculizumab/eculizumab arm), with a mean (95% CI) change in MG-QoL15 total score from ECU-MG-301 Baseline at Weeks 4, 8, and 26 of Study ECU-MG-302 of -13.8 (-18.6, -9.0), -13.2 (-17.9, -8.5), and -14.4 (-22.5, -6.3), respectively.

  In the placebo/eculizumab arm, a change (mean [95% CI]) from ECU-MG-301 Baseline in MG-QoL15 total score was observed at the first follow-up assessment (Week 4; -10.4 [-13.8, -6.9]) of Study ECU-MG-302. The majority of the overall treatment effect was achieved by Week 4 during the Blind Induction Phase, and was sustained through Week 26 (-15.1 [-19.8, -10.4]) (Table 14.2.2.11.1). The magnitude of the improvement in placebo/eculizumab patients at Week 26 in Study ECU-MG-302 from ECU-MG-301 Baseline was similar to that observed in eculizumab-treated patients at Week 26 in Study ECU-MG-301.

Figure 17 Change from Baseline in Myasthenia Gravis Quality of Life 15-item Scale Total Score (Mean and 95% CI) by Treatment Arm over Time from ECU-MG-301

Baseline to Week 26 in Study ECU-MG-302 – Extension Full Analysis Set



Note: 95% CI is based on t-distribution for each treatment arm at each visit.
Abbreviations: BL = Baseline; CI = confidence interval; Ecu = eculizumab; MG-QoL15 = Myasthenia Gravis Quality of Life 15-item scale

Key Tertiary Endpoints

Quality of Life in Neurological Disorders Fatigue Scale

Patients demonstrating improvement from Baseline in Neuro-QoL Fatigue total score with eculizumab treatment during the prior study (Study ECU-MG-301) continued to benefit from eculizumab treatment during Study ECU-MG-302. Through 26 weeks of eculizumab treatment in Study ECU-MG-302, patients consistently sustained the improvement from Baseline in Neuro-QoL Fatigue total score, similar to the improvement evident at Week 26 in Study ECU-MG-301.

Patients receiving placebo in Study ECU-MG-301 who then received eculizumab in Study ECU-MG-302 (placebo/eculizumab arm) showed a clinically meaningful improvement in Neuro-QoL Fatigue total score, which was similar to the response observed for eculizumab-treated patients in Study ECU-MG-301.

Myasthenia Gravis Foundation of America Post-interventional Status

For patients treated with eculizumab in Study ECU-MG-301 who continued into Study ECU-MG-302, 31 (62.0%) reported improvement in their MGFA-PIS after 26 weeks of treatment with eculizumab during Study ECU-MG-301. At Week 26 of Study ECU-MG-302 (52 total weeks of treatment with eculizumab), 14 (93.3%) patients reported improvement in their MGFA-PIS from ECU-MG-301 Baseline.

After 26 weeks of treatment with placebo in Study ECU-MG-301, 20 (41.7%) of the patients who continued into Study ECU-MG-302 reported improvement in their MGFA-PIS. After these patients were enrolled in Study ECU-MG-302 and treated with eculizumab for 26 weeks, 17 (85.0%) reported improvement in their MGFA-PIS from ECU-MG-301 Baseline. No patients in the placebo/eculizumab arm experienced worsening of their MGFA-PIS during Study ECU-MG-302.

A total of 13 (11.5%) patients overall experienced 20 clinical deterioration events; 8 (14.5%) patients in the eculizumab/eculizumab arm experienced 14 clinical deterioration events, and 5 (8.6%) patients in the placebo/eculizumab arm experienced 6 clinical deterioration events. A total of 11 (9.7%) patients overall experienced 18 clinical deterioration events that met the protocol definition provided in Study ECU-MG-301; 7 (12.7%) patients in the eculizumab/eculizumab arm experienced 13 protocol-defined clinical deterioration

events, and 4 (6.9%) patients in the placebo/eculizumab arm experienced 5 protocol-defined clinical deterioration events. One patient experienced MG crisis. All 13 patients with clinical deteriorations required rescue therapy, and IVIg was the most frequently administered rescue therapy.

2.4.3. Supportive study

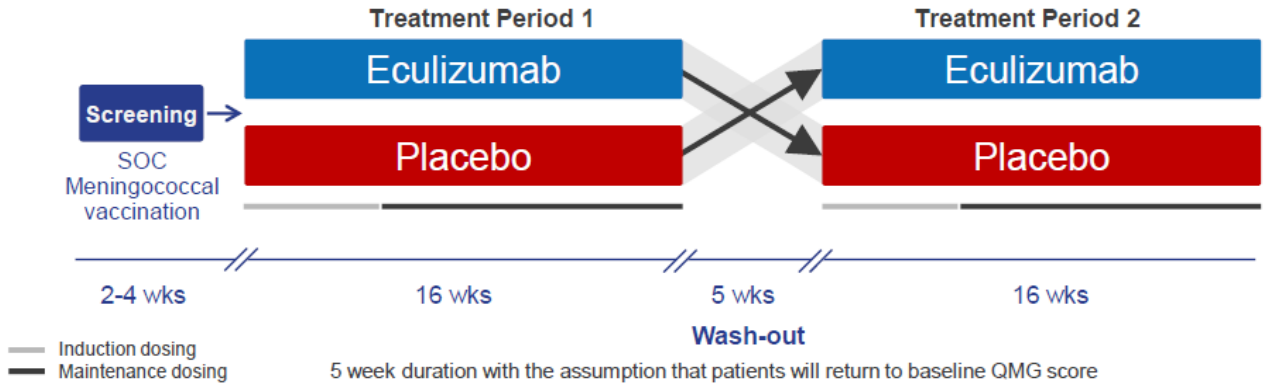
Study C08-001

A Randomized, Double-Blind, Placebo-Controlled, Cross-Over, Multi-Center Study of Eculizumab in Patients with Refractory Generalised Myasthenia Gravis (gMG) who have Moderate to Severe Muscle Weakness Despite Treatment with Immunosuppressants

This was a randomized, double-blind, placebo-controlled, cross-over, multicenter study to evaluate the safety and efficacy of eculizumab for the treatment of patients with refractory gMG.

Patients were followed for 2 to 4 weeks during the Screening Period and then randomised at a 1:1 ratio to receive either eculizumab or placebo for 16 weeks during treatment period 1, followed by a 5-week washout period, and then crossed over for an additional 16 weeks in treatment period 2. Two treatment sequences were used: sequence A, eculizumab to placebo; and sequence B, placebo to eculizumab. The maximum duration of treatment with eculizumab was 16 weeks. All patients received a follow-up phone call 35 days after receiving the last infusion of study drug (eculizumab or placebo).

Figure 18 C08-001 Study Design



Design of the Phase 2 pilot study examining the impact of eculizumab in severe and refractory gMG, including screening (30 days); treatment period 1 (16 weeks); washout (5 weeks); and treatment period 2 (16 weeks).
Abbreviations: gMG = generalised myasthenia gravis; QMG = Quantitative Myasthenia Gravis score for disease severity; SOC = standard of care

Inclusion criteria required a diagnosis of MG based on a positive serologic test for binding anti-AChR Abs at screening and a history of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography (SFEMG) or repetitive nerve stimulation, or a positive anticholinesterase test, or improvement in MG signs on acetylcholinesterase inhibitor. Patients with refractory gMG with prominent clinical symptoms and MGFA Clinical Classification Class II, III or IVa were recruited. A minimum score of 12 in QMG for Disease Severity total score, and of two (2) in ≥4 test items in the QMG for disease severity was required. Patients must have failed treatment or failed to achieve significant clinical benefit with at least two immunomodulators, (i.e. corticosteroids, AZA, cyclosporine, tacrolimus mycophenolic acid, cyclophosphamide, MTX, or IVIG after one year of treatment).

The primary efficacy endpoint was the percentage of patients with a 3-point reduction in QMG Total Score from Baseline to the end of each 16-week treatment period. The dosing regimen administered in Study C08-001 was eculizumab intravenous 600 mg weekly for the first 4 weeks, then 900 mg for the fifth dose (Week 4), followed by 900 mg every 14 ± 2 days.

- **Study Population**

A total of 15 patients qualified for the study, 14 participated in the study, and 11 patients completed the study. One patient discontinued during the Screening Visit, prior to randomization, due to a serious AE.

It should be noted that 14 patients were treated in Period 1 (eculizumab, n = 7; placebo, n = 7) and 12 patients were treated in Period 2 (eculizumab, n = 6; placebo, n = 6). Thus, for the all-treated-patient analysis, there were13 patients treated with eculizumab and 13 patients treated with placebo. Of the 14 patients in this study, all patients (100%) completed and received all study drug infusions in Treatment Period 1. Of the 12 patients that entered Treatment Period 2, 9 patients (75%) received all study drug infusions in Treatment Period 2.

Baseline Characteristics

Key demographic and baseline characteristics are summarized in Table 32 below.

Table 32 Demographics and Baseline Characteristics in Study C08-001

Characteristic	Overall (N = 14)
Gender	
Female	8 (57%)
Male	6 (43%)
Race	
White	11 (79%)
Hispanic	2 (14%)
Black	1 (7%)
Age at Screening (years)	
Mean (SD)	49 (14)
Median (Min-Max)	48 (30 to 72)
Weight at Screening (kg)	
Mean (SD)	87.65 (23.130)
Median (Min-Max)	88.10 (50.5 to 118.5)
Height at Screening (cm)	
Mean (SD)	167.54 (11.118)
Median (Min-Max)	166.00 (152.4 to 185.4)
Body Mass Index (kg/m^2)	
Mean (SD)	31.17 (8.010)
Median (Min-Max)	31.64 (20.2 to 46.9)

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation

At Screening, the majority of patients (57%) were MGFA Class IIIa and nearly all (93%) were receiving at least 1 treatment for MG at the time of screening, with 86% receiving an acetylcholinesterase inhibitor.

Table 33 Myasthenia Gravis Disease History in Study C08-001

Parameter	Overall (N = 14)
MG diagnosis prior to screening (years)	
Mean (SD)	12 (10)
Median (Min;Max)	7 (2;30)
MGFA disease classification at screening, n (%)	
Class IIa	2 (14%)
Class IIb	2 (14%)
Class IIIa	8 (57%)
Class IVa	2 (14%)
QMG total score (LOCF) at screening	
Mean (SD)	19 (6)
Median (Min;Max)	18 (12;36)
MG crisis/exacerbation prior to screening[a]	
Patients with MG crisis/exacerbation prior to screening	12 (86%)
Mean (SD)	5 (6)
Median (Min;Max)	2 (1;19)
Patient MG therapeutic status at screening	
Patients on therapy	13 (93%)
Patients who had thymectomy	6 (43%)
Patients receiving acetylcholinesterase inhibitors	12 (86%)
Patients receiving prednisone	7 (50%)
Patients receiving non-prednisone immunosuppression therapy	7 (50%)
Other therapy	0

a Prior MG crisis/exacerbation was not specified in the enrollment criteria.
Abbreviations: LOCF = last observation carried forward; Max = maximum; MG = myasthenia gravis; Min = minimum; QMG = Quantitative Myasthenia Gravis score for disease severity
Source: Study C08-001 CSR Table 8 (14.1.5)

- **Outcomes and estimation**

Primary Efficacy Endpoint: The primary efficacy endpoint in this study was the percentage of patients with a 3-point reduction from baseline in the QMG total score for disease severity.

Secondary Efficacy Endpoints

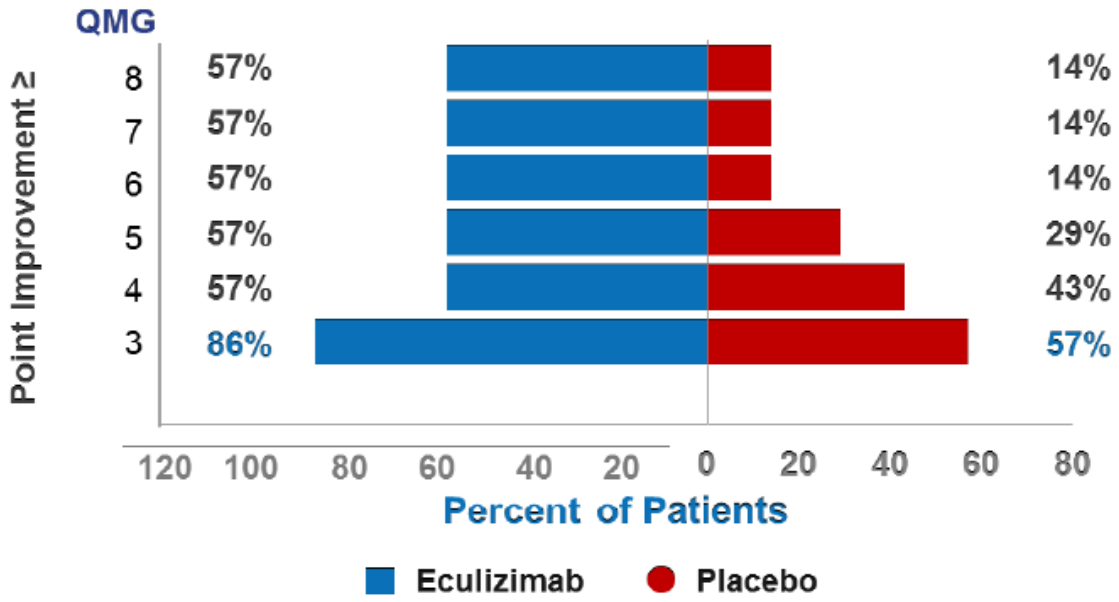
- Change from baseline in the QMG total score for disease severity;
- Change from baseline in the two most affected QMG for disease severity, individual test items;
- Change from baseline in the MGFA-PIS;
- Change from baseline in the MG-ADL profile;
- Change from baseline in respiratory function tests, including spirometry, to characterize the degree of involvement of respiratory muscles;
- Change from baseline in the quality of life (QoL) instrument, Short Form-36.

Primary Efficacy Endpoint

In Treatment Period 1, 86% (6/7) of patients treated with eculizumab had a ≥3-point reduction in QMG total score. In the placebo group, only 4 of 7 patients (57%) had a ≥3-point reduction in QMG total score.

Despite a 5-week washout between each treatment period, patients receiving eculizumab in Period 1 had not returned to their QMG Baseline score by the start of Period 2, suggesting a carryover effect of eculizumab and, thus, making the Period 1 results more relevant to assess the treatment impact of eculizumab, albeit limited to a much smaller number of patients in each treatment arm for the analyses.

Figure 19 Percent of Patients with at Least a Three- to at Least an Eight-Point Change in Quantitative Myasthenia Gravis Total Score in Study C08-001



Proportion of patients with improvement in total score at Week 16 from Baseline
Abbreviations: QMG = Quantitative Myasthenia Gravis score for disease severity
Source: Study C08-001 CSR

Key Secondary Endpoints

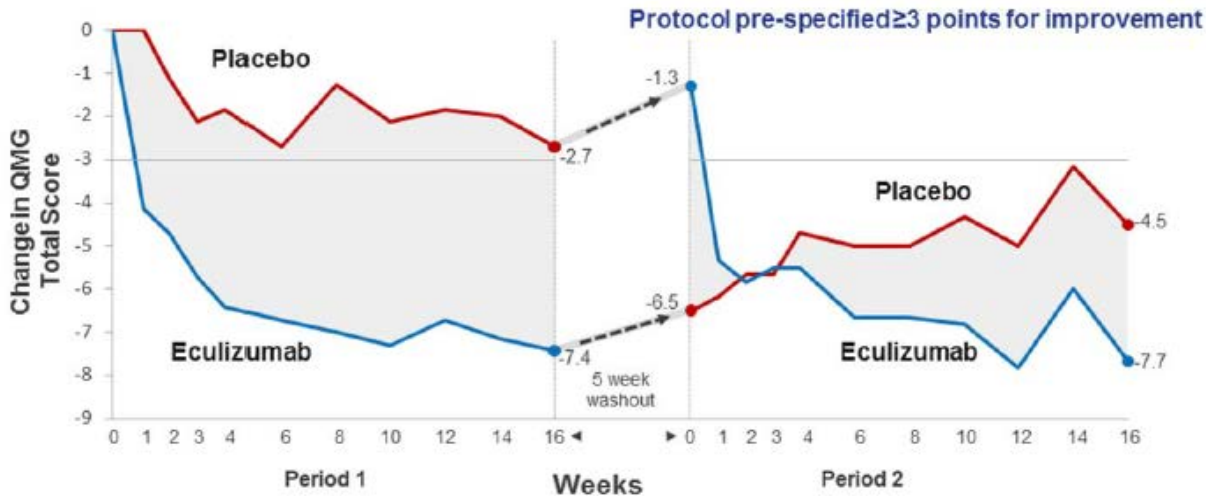
Change from Baseline in Quantitative Myasthenia Gravis Total Score

Based on a paired t-test using patient data at the end of both Treatment Periods, overall change in mean QMG total score was significantly different between eculizumab and placebo (-7.92 versus -3.67; p=0.014). In an additional analysis using a Repeated-Measures mixed model with patient data at all visits, the overall change in mean QMG total score was significantly different between eculizumab and placebo (-6.43 versus -3.18; p<0.0001).

Despite the small sample size of 7 patients per group in Period 1, the change in mean QMG total score from Baseline to last visit in Period 1 demonstrated a trend toward significance between eculizumab (-7.43) versus placebo (-2.71; [analysis of variance p=0.058 with baseline QMG as a covariate and effects for treatment period and sequence]).

The mean changes from Period Baseline in the QMG total score, by eculizumab and placebo treatment are displayed in Figure 20 below.

Figure 20 Change from Baseline in the Quantitative Myasthenia Gravis Total Score for Disease Severity in Study C08-001



Abbreviations: QMG = Quantitative Myasthenia Gravis score for disease severity

Change from Baseline in the Myasthenia Gravis Activities of Daily Living Profile

At the end of Period 1, there was a statistically significant and clinically meaningful difference in the MG-ADL total score between the eculizumab and placebo arms, 4.29 (1.8 SD) versus 7.86 (3.7 SD), respectively; p = 0.041.

Change from Baseline in the Myasthenia Gravis Foundation of America Post-Interventional Status

No eculizumab-treated patients worsened or had any MG exacerbations. Overall, MGFA-PIS for 84.6% (11/13) patients was Improved and for 15.4% (2/13) patients was Unchanged on the last visit during eculizumab treatment, versus 61.5% (8/13) patients Improved and 5/13 (38.5%) Unchanged on the last visit during placebo treatment. In Period 1, MGFA-PIS for 71.4% (5/7) patients was Improved and 28.6% (2/7) Unchanged with eculizumab treatment versus 85.7% (6/7) patients Improved and 14.3% (1/7) Unchanged with placebo treatment.

Other Endpoints

No clinically significant differences were observed in FVC or other measures of pulmonary function, although the number of patients was small.

2.4.4. Discussion on clinical efficacy

The evidence of the efficacy of Soliris (eculizumab) in the treatment of refractory gMG patients is mainly based on data from a 26-week, randomized, placebo controlled Phase 3 study (Study ECU-MG-301). Maintenance of the effect is based on the open-label extension Study ECU-MG-302. The Applicant has submitted the results up to September 2016, as the study is currently ongoing until Year 4. One exploratory Phase 2 study (Study C08-001) provides additional supportive data for this application.

Design and conduct of clinical studies

Study ECU-MG-301 recruited subjects with confirmed diagnosis of gMG (determined by the presence of AChR antibodies and electrophysiological/ pharmacological confirmation) with suboptimal response to multiple immunosuppressive agents with or without routine treatment with chronic plasmapheresis, PE, or IVIg for controlling symptoms.

Only patients with confirmed anti-AchR antibodies ("seropositive" patients) were allowed. Seropositive patients represent approximately 85% of patients with MG. Of the 15% of gMG patients without AChR antibodies, 20–50% have antibodies against muscle-specific tyrosine kinase (MuSK) and against Lrp4 in a minor percentage.

The use of eculizumab (Anti-C5 mAb) in refractory gMG is based on the role of complement activation as one of the effector mechanisms of the condition. Antibodies directed against the AChR bind complement and initiate the complement cascade producing a complement-mediated lysis of the NMJ via formation of membrane attack complexes. Eculizumab blocks the formation of terminal complement complex by selectively preventing the enzymatic cleavage of C5. Whereas anti-AChR antibodies are primarily of the IgG1 and IgG3 isotypes and are thus capable of activating complement, anti-MuSK Abs are predominantly of the IgG4 isotype which is unable to bind complement factor C1q and thus does not cause complement activation. Therefore they would not be a target for eculizumab treatment. A potential target could also be Lrp4, which is predominantly of the IgG1 isotype. At request, the MAH has explained that further investigation is necessary, to elucidate the role of these antibodies in gMG pathogenesis and to understand the clinical consequences of complement inhibition in this population. This has been acknowledged by the CHMP.

The selected dosing regimen was identical to that approved for the treatment of aHUS and supported by PK/PD analyses. At the selected dose 87% of patients achieved complete inhibition (<20% cRBC haemolysis) and 92% reached free C5 concentration of <0.5 μg/ml. The selected period of twenty-six weeks was considered sufficient for the demonstration of short-term efficacy. Given the onset of action and the maximum effect of eculizumab observed in the pilot Phase II, the response was expected to have reached a plateau within the 26 weeks of treatment.

A total of 125 refractory gMG patients were randomized to placebo (n = 63) and eculizumab (n = 62). At entry the majority of patients were concomitantly treated with anticholinesterases (88.8%), corticosteroids (80%), and other immunosuppressants (>80%). Eculizumab or placebo was added on top of patient background therapy and no changes were allowed during the study. This facilitated the interpretability of the results. It was recognised that this add-on trial design is likely to increase the acceptability of the trial, but may create difficulties in showing an additional effect in a population that has been exposed to so many treatment options.

Most of the patients (93.7%) completed the study. In general, demographics and disease characteristics were comparable between the treatment groups. More than half (52.8%) of the patients were classified as Class III followed by 37.6% of Class II (according to The MGFA Clinical Classification) and were symptomatic at baseline (disabling fatigue 82%; difficult arising from a

chair 80%, swallowing difficulty 74%; shortness of breath 73%; speaking difficulties 72%; abnormal pulmonary function tests 54%and abnormal vision 25%).

The evaluation of efficacy was based primarily on the subjective assessment of MG symptoms by the patient (MG-ADL) and secondarily by the quantitative evaluation of relevant muscle groups by the physician (QMG). Several related definitions of responders were used as secondary endpoints. Other specific scales (MGC Scale) and the impact of the change in the QoL (MG-QoL15) were also assessed. The selected endpoints are validated standard methods for evaluation of MG and have been previously used in several clinical studies in this condition.

Efficacy data and additional analyses

In the primary analysis of changes in MG-ADL score at Week 26 (Worst-Rank ANCOVA) no statistically significant difference was shown for the eculizumab treatment regimen when compared against placebo (p=0.0698). Overall, a decrease of 4.7 points was observed in the eculizumab arm versus 2.8 points in the placebo group with substantially overlapping confidence intervals. The main effect was observed in the first 12 weeks of treatment with little additional benefit afterwards. Statistically significant differences were achieved in the pre-specified sensitivity analyses (ANCOVA and Repeated-Measured) although the effect size of all the conducted analyses was smaller than the 2-point reduction a priori defined as clinically relevant.

In the primary Worst-Rank score analysis a total of 22 patients (12 on placebo, 10 on eculizumab) were assigned to the death (none)/MG Crisis/rescue/discontinuation group according to the final agreed SAP (Version 3.0). This assignment was irrespective of whether the criteria for clinical deterioration were met or not. The Applicant later submitted data from an additional analysis in which patients who discontinued were assigned to rescue group only if they met the criteria for MG clinical deterioration, and the nominal p-value of the Worst-Rank analysis of the primary endpoint was p=0.0140. The Applicant justified this approach with the fact that this analytic approach was the one established in the previous SAP Version 2.0 (and therefore pre-specified) and that it was to be considered more informative. This justification was acknowledged, however it should be taken into consideration that this analysis was abandoned (in agreement with the regulatory authorities) and that in the context of this assessment it can be considered with a similar value to that of a post-hoc analysis. Furthermore, this analysis could be considered to provide a better estimation of the eculizumab activity *per se* but was not judged to be the optimal one to assess the actual benefit of treatment at a population level, ie, the scenario where discontinuations due to safety reasons should be taken on board in the methodology of the analysis. This complementary information does not fully alleviate the main uncertainty related with the clinical relevance of the observed effect.

Statistically significant differences were observed in the main secondary endpoint (QMG score) although the 3-point difference defined as a clinically significant treatment effect was not evident until Week 26. It has to be noted though, that literature data are not unanimous on this aspect and according to some authors a fall in QMG score of 4 points or more is considered the reference of significant clinical improvement[10].

One of the relevant issues observed in the data was that the placebo group appeared to show a greater than predicted response when measured by the patients (MG-ADL) in comparison to the one measured by physicians (QMG). Overall, the expected change from baseline in the placebo group was -1.5 points for MG-ADL and -3 points for QMG total score from baseline (sample size estimation). At Week 26 the reductions observed in the placebo were - 2.8 points in MG-ADL score and -2.4 in QMG total score. A sizeable

[10]Sanders DB et al. Does change in acetylcholine receptor antibody level correlate with clinical change in myasthenia gravis? Muscle Nerve 2014; 49: 483-486

percentage of patients in the placebo group fell within the definition of responders: 40% (versus 60% in eculizumab group) achieved a better control of symptoms under patient's perspective (MG-ADL) and 19% (versus 45% of patients on eculizumab) had a meaningful improvement in the evaluation performed by the physicians (QMG total score).

It is not clear whether these findings can be attributed to the patients' expectations of a benefit when participating in a clinical trial, the regression to the mean, or the fluctuating nature of the disease. Regardless, it was surprising that in such a refractory population, with limited room for improvement considering the lack of options to treatment adjustment, such perceived improvement was registered. The Applicant provided an analysis including a number of clinical trials in MG reported in literature in which similar placebo effect was shown. Whereas differences in intervention, number of patients, severity of the condition, concomitant treatment do not allow direct comparisons to Study ECU-MG-301, these offered a credible explanation to the placebo effect reported in Study MG-ECU-301.

Initially the CHMP expressed concerns about the magnitude of the effect observed on the MGs scales, as its clinical relevance was not clear. Several different mechanisms have been described as involved in MG pathogenesis eg, direct blockade of acetylcholine binding sites by the antibodies (Abs) or the induction of endocytosis and degradation of AchRs (for which eculizumab is not an option), and the relative contribution of each to the severity and symptomatology remains unknown. Thus, it may be logical to assume that this may provide one possible explanation for the magnitude of the effect as it has been achieved when targeting only one of the pathogenic mechanisms. In an effort to provide an alternative explanation, the Applicant discussed and compared the results in terms of the Minimal Clinically Important Difference (MCID) with the ones reported in literature for the efficacy variables and in terms of responder rates. They provided a justification for the MCID at individual level (absolute change from baseline in individual patients) rather than as a measure of average difference between groups. Although not optimal, this was considered a valid approach to evaluate and position the expected treatment effect of the product. Of note, a difference of 2.5 in mean changes from baseline for MG-ADL (mean change from baseline of 4 for eculizumab and 1.5 for placebo) was assumed in the sample size estimation.

The main secondary endpoint QMG provided more robust results since a more clear separation between groups was observed in all of the conducted analyses. However, this outcome was not time-weighted as scores at intermediate time points were ignored, and this could be of interest in a fluctuating condition. These time aspects are partially informed by the patient-reported MG-ADL score, given that it provides information over the prior 7 days. In relation to this issue, the responder rates reported through the study showed a regular effect during the 26 week-study period both from the patient's (MG-ADL) and physician's perspective.

Another important point that was considered in the judgement whether the observed treatment effect can be seen to reflect a clinically relevant improvement was assessed in a QoL questionnaire
(MG-QoL 15). There an improvement was observed in both groups (-6.5 in placebo and -13.5 in patients treated with eculizumab). This difference was statistically significant both in the primary analysis (Worst-Rank ANCOVA p=0.0281) and in the sensitivity analyses.

In the discussion on what constitutes a relevant clinical effect, it also needs to be pointed out that the magnitude of change required to indicate an improvement or worsening of the condition, is variable and depends on the severity of MG[11]. As reference, the 3-point reduction in the MGC (considered as clinically relevant) would correspond to a mean improvement in MG-QoL15 score by 12 points. Similarly, in a randomized trial comparing IVIg and plasmapheresis, the impact on QoL was assessed according a definition of response in terms of QMG reduction. Both IVIg and plasmapheresis patients showed similar reduction in QMG scale and mean six- to nine-point improvements in MGQoL15 scores after treatment. Once again, the

[11]Myasthenia Gravis Fundation of America http://www.myasthenia.org/HealthProfessionals/EducationalMaterials.aspx

magnitude of the observed differences in QoL questionnaires is on the verge of what could be considered clinically relevant. In an attempt to further justify the relevance, the applicant provided a review of literature in order to address the clinical relevance of the results obtained in Study MG-ECU-301. In several papers a 7- to 8-point change over baseline has been established as clinically meaningful. Both placebo and eculizumab groups showed a score reduction (QoL improvement) with respect to baseline. The improvement experienced by patients treated with eculizumab clearly surpasses this magnitude. The change in placebo group almost reached this magnitude. As a complementary support the effect on MG-QoL15 individual items have been examined. A clear separation between eculizumab and placebo has been observed in most of them. The change at Week 26 was below the pre-defined response threshold (0.5) in 10 out of 15 items in the placebo group and none of the items in eculizumab group was <0.5, and that was considered reassuring. While the magnitude of change was beyond the clinical meaningfulness (as defined in literature) for eculizumab, this was not the case for placebo. This difference was also confirmed at individual item level. MG-QoL results are congruent with the clinical endpoints and provide additional dimension to clinical results, making the global data more complete and reassuring.

Supplementary information from PD parameters did not provide further insight in order to elucidate the effect or identify a population where the benefit could be more compelling. Examination by subgroups was also not informative so that there did not seem to be a population (according disease severity, different background therapy etc.) in which a more prominent effect could be clearly identified.

No correlation could be established between AChR Ab levels during the study and the response to treatment. This is however consistent with what is described in literature and additional work is required before Ab levels can be considered a reliable biomarker for monitoring clinical status or treatment response. Also, no relationship was observed between eculizumab exposure and MG-ADL, QMG, MGC, or clinical deterioration.

With respect to long-term efficacy data, only preliminary results were available at the time of this report. Study ECU-MG-302 (4 year duration) is ongoing and the MAH submitted the data from an interim analysis performed as of the cut-off date of 21 Sep 2016. Results from the interim analysis indicate a positive effect on the maintenance of the response to eculizumab. When patients who received placebo in the Study ECU-MG-301 were treated with eculizumab in Study ECU-MG-302 an improvement similar to that showed by patients on active treatment in the previous study was observed. In patients previously treated with eculizumab the response was consistently maintained through Study ECU-MG-302. Also at Week 26 of the study responder rates were similar between both treatment arms (MG-ADL: eculizumab/eculizumab 65.3% versus placebo/eculizumab 69.1% (Table 30); QMG: eculizumab/eculizumab 43.8% versus placebo/eculizumab 47.3%(Table 31)).

Eculizumab (or placebo) was added on top of patient background therapy. The majority of patients were receiving concomitant treatment at entry (76.1% were taking prednisone and 83.8% were taking ≥1 IST other than prednisone). During this extension study the concomitant treatment could be adapted. In this setting, a decrease of the daily dose of at least 1 immunosuppressant was observed in 47% of patients with the most common reason for change being improvement in MG symptoms while on eculizumab treatment. It cannot be predicted if the observed IST-sparing effect will be waned with longer exposure.

2.4.1. Conclusions on the clinical efficacy

Evidence of the efficacy of Soliris (eculizumab) in the treatment of adult patients with refractory (gMG) has been demonstrated, despite the absence of statistical significance in the primary endpoint. The results of the secondary variables and the exploratory analyses carried out on the primary endpoint are considered confirmatory of a true effect of eculizumab. The use of the Worst Rank method in the primary analysis likely affected the results, as a very conservative approach. Regardless of the fact that the clinical relevance of the observed effect has not been thoroughly elucidated, it has been shown that the use of eculizumab on top of

applied background therapy provides a clear benefit. Maintenance of effect still remains to be confirmed by long term data and a study aimed to resolve this uncertainty is currently ongoing.

The following measures are considered necessary to address issues related to clinical efficacy:

The applicant should submit annual updates of the open-label extension Study ECU-MG-302. Final study results should be provided when available to confirm long term efficacy and safety.

2.5. Clinical safety

Introduction

The evaluation of the safety of eculizumab in the treatment of patients with refractory gMG is based on data from the 3 studies included in this application (Table 1).

The safety data are presented for the Safety Set (ie, all patients who received at least one dose of study drug [either eculizumab or placebo]) for the 3 clinical studies included in this development program.

Data in this summary are reported by individual study, with data from the Phase 3 studies (Study ECU-MG-301 and Study ECU-MG-302) presented side-by-side and data from the Phase 2 study (Study C08-001) presented separately.

Data from the Phase 3 studies were not pooled, as Study ECU-MG-302 is an extension study of Study ECU-MG-301 and, therefore, the population is a subset of the population included in the first Phase 3 study. The Phase 2 study was a cross-over study and used a different dosing regimen from that used in the Phase 3 studies. For these reasons, it is not pooled with the Phase 3 studies.

Additionally, eculizumab is approved for use in PNH and aHUS. Safety data from clinical trials and the postmarketing setting in these indications provide additional information for assessing the safety of eculizumab (Periodic Safety Update Report 14 data cut of 01 Oct 2016).

In this clinical development program, AEs were defined as any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition, and abnormal laboratory findings that are considered to be of clinical significance were to be considered AEs. Medication errors and uses outside what was foreseen in the protocol, including misuse and abuse of the study drug, were also to be considered AEs.

Serious adverse events were defined as any AE that fulfils at least 1 of the following criteria:

1. Results in death
2. Is life-threatening
3. Requires hospitalization or prolongation of existing hospitalization (including transfer within a hospital to receive more intense medical/surgical care)
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect
6. Is an important medical event

Treatment-emergent AEs (TEAEs) are AEs with onset, or worsening, on or after the first dose of study drug. Treatment-emergent SAEs (TESAEs) are SAEs with onset, or worsening, on or after the first dose of study drug.

Adverse events of special interest (AESIs) were based on clinical and postmarketing data of eculizumab in other indications, along with data from the early clinical development of eculizumab in refractory gMG patients. Adverse events of special interest for this submission include infections (meningococcal infections, aspergillus infections, and any serious infection), sepsis, infusion-related reactions, serious cutaneous reactions, cardiac disorders, and angioedema.

Treatment-emergent AEs/SAEs were summarized by treatment arm and by age, gender, race, and geographic region for Study ECU-MG-301. Region categories included North America, South America, Europe, Asia-Pacific, and Japan. Age groups (at first study drug dose in Study ECU-MG-301) were defined as 18 to 65 years and > 65 years.

Patient exposure

A total of 133 adult patients with refractory gMG were treated with eculizumab in these three studies combined. In Study ECU-MG-301, 62 patients were treated with eculizumab, while the remaining 63 were treated with placebo. A total of 117 patients from the 125 treated in Study ECU-MG-301 continued into the extension study (Study ECU-MG-302), 113 of whom had been treated with eculizumab in the extension study as of 01 Mar 2016 (the clinical database cut-off date for this interim analysis) and were included in the first interim analysis. These 113 patients included 58 patients from the placebo arm and 55 patients from the eculizumab arm in Study ECU-MG-301. In Study C08-001, a total of 13 patients received eculizumab.

The study duration of patients in the Safety Set of Study ECU-MG-301 was similar in each treatment arm . Patients in the eculizumab arm received treatment over a median (range) duration of 183.0 days (22−197 days). In Study ECU-MG-302, the study duration and duration of treatment were also similar in the two treatment arms. The median (range) duration of treatment was 108.5 days (1−462 days) in the placebo/eculizumab arm and 125.0 days (1−449 days) in the eculizumab/eculizumab arm. As of the clinical database cut-off date of 01 Mar 2016, there were 37 patients overall (N = 20 in the placebo/eculizumab arm and N = 17 in the eculizumab/eculizumab arm) who were treated for at least 26 weeks as part of Study ECU-MG-302.

The patient years of exposure for each treatment arm in Study ECU-MG-302 was slightly less (24.9 for the placebo/eculizumab arm, and 22.2 for the eculizumab/eculizumab arm) than the patient years of exposure for the eculizumab arm in Study ECU-MG-301 (29.6). For patients in the eculizumab/eculizumab arm of Study ECU-MG-302, the total patient years of exposure for Studies ECU-MG-301 and ECU-MG-302 combined is 52.0.

Table 34 Duration of Treatment in Studies ECU-MG-301 and ECU-MG-302 Side-by-Side – Safety Set

	Study ECU-MG-301		Study ECU-MG-302		
	Placebo N = 63	Eculizumab N = 62	Placebo/ Eculizumab N = 58	Eculizumab/ Eculizumab N = 55	Total N = 113
Study Duration					
Mean (SD) (days)	214.4 (37.82)	204.8 (33.04)	167.8 (152.70)	159.4 (138.76)	163.7 (145.49)
Median (days)	211.0	210.0	131.0	127.0	128.0
Min, Max (days)	47, 378	65, 301	1, 490	2, 463	1, 490
Total	13506	12700	9730	8767	18497
Patient Years of Exposure	31.1	29.6	24.9	22.2	47.1
Duration of Treatment with Study Drug (Eculizumab or Placebo)					
Mean (SD) (days)	180.5 (26.37)	174.5 (33.44)	156.5 (150.07)	147.5 (138.91)	152.1 (144.17)
Median (days)	183.0	183.0	108.5	125.0	118.0
Min, Max (days)	22, 206	22, 197	1, 462	1, 449	1, 462
Total	11370	10822	9077	8112	17189
Number of Supplemental Infusions					
Mean (SD)	0.3 (1.54)	0.1 (0.59)	0.1 (0.66)	0.0 (0.19)	0.1 (0.49)
Median	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 12	0, 4	0, 4	0, 1	0, 4
Total Infusions	18	8	8	2	10
Total Dose (mg)					
Mean (SD)	0.000 (0.0000)	17205.081 (2923.9952)	15345.431 (13269.2968)	13500.000 (11807.2012)	14447.212 (12557.1950)
Median	0.000	18000.000	12600.000	10800.000	12000.000
Range	0.00, 0.00	3550.00, 19200.00	900.00, 42000.00	1200.00, 38400.00	900.00, 42000.00
Total Number of Patients with a Dose Interrupted During the Study					
n (%)	11 (17.5)	5 (8.1)	2 (3.4)	4 (7.3)	6 (5.3)

Abbreviations: Max = maximum; Min = minimum

Study duration and treatment duration in Study ECU-MG-302 from the 21 Sep 2016 clinical database cut-off are provided the table below. The median (range) duration of treatment with eculizumab for the placebo/eculizumab and eculizumab/eculizumab arms is 40.1 weeks (12.1 to 96.0 weeks) and 40.6 weeks (1 day to 92.1 weeks), respectively. Patients in the eculizumab/eculizumab arm had received an additional 26 weeks of treatment with eculizumab in Study ECU-MG-301, prior to enrolling in Study ECU-MG-302. In Studies ECU-MG-301 and ECU-MG-302 combined, 113 (91.9%) patients had been exposed to eculizumab for > 6 months and 72 (58.5%) patients had been exposed to eculizumab for > 12 months.

Table 35 Study Duration and Treatment Duration by Treatment Arm in Study ECU-MG-302 – Extension Safety Set

Variable	Statistic	Placebo/Eculizumab (N = 61)	Eculizumab/Eculizumab (N = 56)	Total (N = 117)
Study Duration (days)[a]	n	61	56	117
	Mean (SD)	349.7 (160.64)	339.3 (155.10)	344.7 (157.42)
	Median	294.0	292.5	294.0
	Min, Max	111, 694	78, 667	78, 694
	Total	21333	18999	40332
Duration of Treatment (days)[b]	n	61	56	117
	Mean (SD)	336.8 (159.65)	325.8 (159.55)	331.5 (159.01)
	Median	281.0	284.5	281.0
	Min, Max	85, 672	1, 645	1, 672
	Total	20546	18242	38788

a Study Duration = Date of Completion/Discontinuation (or death) - Date of Informed Consent + 1.
b Duration of Treatment = Last IP Dose Date - First IP Dose Date + 1.
Abbreviations: IP = investigational product; Max = maximum; Min = minimum

Exposure to the study drug in Study C08-001 is summarized in Table 36. Of the 13 total patients treated with eculizumab, 7 of whom were treated prior to crossing over to placebo and 6 of whom were treated after crossing over from placebo, all received 11 infusions and the median (range) duration of treatment was 16.1 weeks (16.0–16.6 weeks). The total amount of eculizumab that each patient received over the course of the study was 8700 mg.

Table 36 Duration of Treatment in Study C08-001 – Safety Population

	Eculizumab Overall	Placebo Overall
Duration of therapy (weeks)		
n	13	13
Mean (SD)	16.2 (0.1)	15.1 (4.3)
Median (Min, Max)	16.1 (16.0, 16.6)	16.1 (1.1, 17.4)
Number of doses		
n	13	13
Mean (SD)	11.0 (0)	10.2 (2.5)
Median (Min, Max)	11.0 (11.0, 11.0)	11.0 (2.0, 11.0)
Total amount of study drug infused (mg)		
n	13	13
Mean (SD)	8700 (0)	0 (0)
Median (Min, Max)	8700 (8700, 8700)	0 (0, 0)

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation

- **Demographic and Other Characteristics of Study Population**

There were no differences between treatment arms in the demographic characteristics of gender, age at first dose of study drug, ethnicity, weight, height, or body mass index (BMI) in Study ECU-MG-301. The majority of patients in the study were white (53 [85.5%] patients in the eculizumab arm and 42 [66.7%] patients in the placebo arm).

There was an apparent difference between the two arms in regard to race and region, as overall only 3 (4.8%) patients in the eculizumab arm were Asian while 16 (25.4%) patients in the placebo arm were Asian. Only 6 (4.8%) patients overall were in each of Class IVa and Class IVb, while the majority of patients were in Class IIa, IIb, IIIa, or IIIb.

Patients in this study had either failed 2 or more ISTs or had used IVIg, or both. Over half of the total patients had tried or failed at least 3 concomitant ISTs and the majority had tried or failed IVIg. Over half of the patients (54.4%) enrolled in Study ECU-MG-301 post-thymectomy (37 [59.7%] patients in the eculizumab arm, and 31 [49.2%] patients in the placebo arm).

Table 37 Demographics and Baseline Characteristics in Studies ECU-MG-301 and ECU-MG-302 Side-by-Side

Variable	Statistic	Study ECU-MG-301			Study ECU-MG-302		
		Placebo N = 63	Eculizumab N = 62	Total N = 125	Placebo/Eculizumab N = 58	Eculizumab/Eculizumab N = 55	Total N = 113
Age at First Study Drug Dose (years)[a]	Mean (SD)	46.9 (17.98)	47.5 (15.66)	47.2 (16.80)	47.8 (17.99)	46.9 (15.49)	47.4 (16.75)
	Median	48.0	44.5	46.0	49.5	44.0	45.0
	Min, Max	19, 79	19, 74	19, 79	19, 80	20, 75	19, 80
Gender							
Male	n (%)	22 (34.9)	21 (33.9)	43 (34.4)	20 (34.5)	17 (30.9)	37 (32.7)
Female	n (%)	41 (65.1)	41 (66.1)	82 (65.6)	38 (65.5)	38 (69.1)	76 (67.3)
Ethnicity							
Hispanic or Latino	n (%)	10 (15.9)	8 (12.9)	18 (14.4)	9 (15.5)	8 (14.5)	17 (15.0)
Not Hispanic or Latino	n (%)	50 (79.4)	51 (82.3)	101 (80.8)	46 (79.3)	44 (80.0)	90 (79.6)
Not Reported	n (%)	0 (0.0)	2 (3.2)	2 (1.6)	0 (0.0)	2 (3.6)	2 (1.8)
Unknown	n (%)	3 (4.8)	1 (1.6)	4 (3.2)	3 (5.2)	1 (1.8)	4 (3.5)
Race							
Asian	n (%)	16 (25.4)	3 (4.8)	19 (15.2)	15 (25.9)	3 (5.5)	18 (15.9)
Black or African American	n (%)	3 (4.8)	0 (0.0)	3 (2.4)	2 (3.4)	0 (0.0)	2 (1.8)
White	n (%)	42 (66.7)	53 (85.5)	95 (76.0)	39 (67.2)	46 (83.6)	85 (75.2)
Multiple	n (%)	0 (0.0)	1 (1.6)	1 (0.8)	0 (0.0)	1 (1.8)	1 (0.9)
Unknown	n (%)	0 (0.0)	1 (1.6)	1 (0.8)	0 (0.0)	1 (1.8)	1 (0.9)
Other	n (%)	2 (3.2)	4 (6.5)	6 (4.8)	2 (3.4)	4 (7.3)	6 (5.3)
Is the Patient of Japanese Descent?							
Yes	n (%)	9 (14.3)	3 (4.8)	12 (9.6)	8 (13.8)	3 (5.5)	11 (9.7)
No	n (%)	54 (85.7)	59 (95.2)	113 (90.4)	50 (86.2)	52 (94.5)	102 (90.3)
Weight (kg)	n	63	62	125	ND	ND	ND
	Mean (SD)	86.24 (28.072)	87.67 (28.190)	86.95 (28.026)	ND	ND	ND
	Median	83.10	80.00	80.70	ND	ND	ND
	Min, Max	37.0, 155.5	42.9, 173.6	37.0, 173.6	ND	ND	ND
Height (cm)	n	63	62	125	ND	ND	ND
	Mean (SD)	167.07 (9.383)	166.63 (9.684)	166.85 (9.497)	ND	ND	ND
	Median	167.50	165.10	166.70	ND	ND	ND
	Min, Max	139.7, 184.2	150.1, 186.2	139.7, 186.2	ND	ND	ND
BMI (kg/m^2)[b]	n	63	62	125	ND	ND	ND
	Mean (SD)	30.53 (8.373)	31.37 (8.997)	30.94 (8.663)	ND	ND	ND
	Median	30.67	30.15	30.67	ND	ND	ND
	Min, Max	17.5, 51.1	14.8, 52.6	14.8, 52.6	ND	ND	ND
MGFA Class at Screening							
Class IIa	n (%)	15 (23.8)	10 (16.1)	25 (20.0)	ND	ND	ND
Class IIb	n (%)	14 (22.2)	8 (12.9)	22 (17.6)	ND	ND	ND
Class IIIa	n (%)	16 (25.4)	20 (32.3)	36 (28.8)	ND	ND	ND
Class IIIb	n (%)	13 (20.6)	17 (27.4)	30 (24.0)	ND	ND	ND
Class IVa	n (%)	2 (3.2)	4 (6.5)	6 (4.8)	ND	ND	ND
Class IVb	n (%)	3 (4.8)	3 (4.8)	6 (4.8)	ND	ND	ND
MGFA Class Randomization Stratification							
Class IIa or IIIa	n (%)	32 (50.8)	30 (48.4)	62 (49.6)	ND	ND	ND
Class IVa	n (%)	2 (3.2)	4 (6.5)	6 (4.8)	ND	ND	ND
Class IIb or IIIb	n (%)	26 (41.3)	25 (40.3)	51 (40.8)	ND	ND	ND
Class IVb	n (%)	3 (4.8)	3 (4.8)	6 (4.8)	ND	ND	ND

a Age = (Date of First IP Dose in that Particular Study – Date of Birth) / 365.25
b BMI (kg/m2) = Weight (kg) / [Height (cm) / 100]2
Abbreviations: BMI = body mass index; MGFA = Myasthenia Gravis Foundation of America; ND = not determined

Demographics and baseline characteristics of patients in Study C08-001 are summarized in Table 32. Of the 14 patients enrolled, 8 (57%) were female and 6 (43%) were male. The majority (11/14 [79%]) were white. At Screening, the majority of patients (57%) had an MGFA MG disease classification of IIIa. The median (range) duration of MG disease from diagnosis to screening was
7 years (2−30 years). Nearly all (93%) patients were receiving at least one or more treatments for MG at the time of screening: 86% (12/14) were receiving an acetylcholinesterase inhibitor, 50% (7/14) were receiving prednisone, 50% (7/14) were receiving non-prednisone IST, and 43% (6/14) patients were status post-thymectomy for at least 12 months prior to screening.

Adverse events

Of the 125 patients in the Safety Set of Study ECU-MG-301, 109 patients (87.2%) reported a total of 767 AEs. The incidence of AEs was higher in the placebo arm (406 events reported by 56 [88.9%] patients) than in the eculizumab arm (361 events reported by 53 [85.5%] patients). The number and percentage of patients with non-SAEs was similar (52 [83.9%] patients in the eculizumab arm and 53 [84.1%] patients in the placebo arm).

In the patients who continued into Study ECU-MG-302, events were experienced by 42 (72.4%) patients in the placebo/eculizumab arm and 38 (69.1%) patients in the eculizumab/eculizumab arm.

Table 38 Overview of Treatment-Emergent Adverse Events in Studies ECU-MG-301 and ECU-MG-302 Side-by-Side –Safety Set

Adverse Event Category	Study ECU-MG-301				Study ECU-MG-302					
	Placebo N = 63		Eculizumab N = 62		Placebo/ Eculizumab N = 58		Eculizumab/ Eculizumab N = 55		Total N = 113	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Adverse Events (AEs)	406	56 (88.9)	361	53 (85.5)	263	42 (72.4)	228	38 (69.1)	491	80 (70.8)
Related	141	25 (39.7)	109	30 (48.4)	101	19 (32.8)	63	18 (32.7)	164	37 (32.7)
Not Related	265	55 (87.3)	252	49 (79.0)	162	38 (65.5)	165	30 (54.5)	327	68 (60.2)
Mild	280	52 (82.5)	264	49 (79.0)	191	40 (69.0)	164	34 (61.8)	355	74 (65.5)
Moderate	98	34 (54.0)	74	26 (41.9)	60	17 (29.3)	46	19 (34.5)	106	36 (31.9)
Severe	28	16 (25.4)	23	8 (12.9)	12	6 (10.3)	18	9 (16.4)	30	15 (13.3)
AEs leading to withdrawal	ND	0 (0.0)	ND	4 (6.5)	ND	1 (1.7)	ND	1 (1.8)	ND	2 (1.8)
Serious Adverse Events (SAEs)	33	18 (28.6)	17	9 (14.5)	11	9 (15.5)	16	9 (16.4)	27	18 (15.9)
Related	2	2 (3.2)	10	5 (8.1)	5	5 (8.6)	6	3 (5.5)	11	8 (7.1)
Not Related	31	16 (25.4)	7	5 (8.1)	6	5 (8.6)	10	6 (10.9)	16	11 (9.7)
SAEs leading to withdrawal	ND	0 (0.0)	ND	4 (6.5)	ND	1 (1.7)	ND	1 (1.8)	ND	2 (1.8)
Deaths	ND	0 (0.0)	ND	0 (0.0)	ND	0 (0.0)	ND	0 (0.0)	ND	0 (0.0)

Abbreviations: AE = adverse event; ND = not determined; SAE = serious adverse event

An overview of TEAEs in Study C08-001 is provided in Table 39. Overall, 13 (100%) patients had at least 1 AE while receiving eculizumab and 11 (84.6%) patients had at least one AE while receiving placebo. Most AEs were mild to moderate in severity, and an equal number of severe AEs were reported for patients on eculizumab compared to placebo. There were no reported AEs that were definitely related to the study drug.

Table 39 Overview of Treatment-Emergent Adverse Events in Study C08-001 – Safety Population

Category	Eculizumab			Placebo		
	Treatment Period 1 (N = 7) n (%)	Treatment Period 2 (N = 6) n (%)	Overall (N = 13) n (%)	Treatment Period 1 (N = 7) n (%)	Treatment Period 2 (N = 6) n (%)	Overall (N = 13) n (%)
Patients with no AEs	0	0	0	2 (28.6)	0	2 (15.4)
Patients with at least 1 AE	7 (100.0)	6 (100.0)	13 (100.0)	5 (71.4)	6 (100.0)	11 (84.6)
Patients with at least 1 SAE	1[a] (14.3)	0	1 (7.7)	0	1[a] (16.7)	1 (7.7)
Patients discontinued due to AE	0	0	0	0	0	0
Patients with AE leading to death	0	0	0	0	0	0
AE severity						
Mild	2 (28.6)	0	2 (15.4)	1 (14.3)	3 (50.0)	4 (30.8)
Moderate	3 (42.9)	4 (66.7)	7 (53.8)	3 (42.9)	1 (16.7)	4 (30.8)
Severe	2 (28.6)	2 (33.3)	4 (30.8)	1 (14.3)	2 (33.3)	3 (23.1)
AE relationship						
Unrelated	1 (14.3)	5 (83.3)	6 (46.2)	1 (14.3)	4 (66.7)	5 (38.5)
Possible	5 (71.4)	1 (16.7)	6 (46.2)	4 (57.1)	1 (16.7)	5 (38.5)
Probably	1 (14.3)	0	1 (7.7)	0	1 (16.7)	1 (7.7)
Definite	0	0	0	0	0	0

Notes: 1 AE occurrence per patient was counted for each category. If an AE occurred between the first dose administration of study drug (eculizumab or placebo) and Visit 14 dose, the AE was classified under Treatment Period 1; otherwise, it was classified under Treatment Period 2. Any AE that occurred during the 2-week Wash-Out Period was classified under Treatment Period 1. a One patient experienced 2 SAEs, 'MG exacerbation' and 'MG crisis', during the Wash-Out Period and Treatment Period 2,respectively. AEs that occurred during the Wash-Out Period are reported in Treatment Period 1.
Abbreviations: AE = adverse event; MG = myasthenia gravis; SAE = serious adverse event

- **Common Adverse Events**

In Study ECU-MG-301, a total of 767 AEs (eculizumab arm: 361; placebo arm: 406) were reported. Fifty-three (85.5%) patients in the eculizumab arm and 56 (88.9%) patients in the placebo arm reported AEs. In both treatment arms, the most frequently reported AEs in order of descending frequency were headache, upper respiratory infection, nasopharyngitis, myasthenia gravis, nausea, diarrhoea, back pain, dizziness, urinary tract infection, vomiting, contusion, insomnia, myalgia, paresthesia, oedema peripheral, pain in extremity, pyrexia, chills, neck pain, oral herpes, and pruritus. Treatment-emergent AEs of myasthenia gravis were reported by 6 (9.7%) patients in the eculizumab arm and 11 (17.5%) patients in the placebo arm.

Similar to Study ECU-MG-301, the most frequently reported AEs by patients who continued into Study ECU-MG-302 were nasopharyngitis (20 [17.7%] patients overall; 10 [17.2%] patients in the placebo/eculizumab arm and 10 [18.2%] patients in the eculizumab/eculizumab arm) and headache (19 [16.8%] patients overall; 13 [22.4%] patients in the placebo/eculizumab arm and 6 [10.9%] patients in the eculizumab/eculizumab arm). The incidence of upper respiratory tract infection was higher in Study ECU-MG-301 (17.6% overall), compared to Study ECU-MG-302 (5 [4.4%] patients overall; 3 [5.2%] patients in the placebo/eculizumab arm and 2 [3.6%] patients in the eculizumab/eculizumab arm).

Common AEs in Study C08-001 that occurred in ≥3 patients were nausea, back pain, nasopharyngitis, myalgia, neck pain, headache, and cough (Table 12). Overall, 7 patients reported AEs in the Infections and Infestations system organ class (SOC) while receiving eculizumab compared to 12 patients receiving placebo.

Table 40 Treatment-Emergent Adverse Events by Preferred Term and Treatment Arm in Studies ECU-MG-301 and ECU-MG-302 Side-by-Side (Events Occurring in ≥5% of Patients in Either Treatment Arm in Either Study) – Safety Set

	Study ECU-MG-301		Study ECU-MG-302		
	Placebo N = 63	Eculizumab N = 62	Placebo/ Eculizumab N = 58	Eculizumab/ Eculizumab N = 55	Total N = 113
Patient Years of Exposure	31.1	29.6	24.9	22.2	47.1
Preferred Term, n (%)					
Arthralgia	3 (4.8)	1 (1.6)	2 (3.4)	3 (5.5)	5 (4.4)
Back pain	6 (9.5)	5 (8.1)	3 (5.2)	2 (3.6)	5 (4.4)
Chills	4 (6.3)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Contusion	2 (3.2)	5 (8.1)	2 (3.4)	4 (7.3)	6 (5.3)
Cough	3 (4.8)	1 (1.6)	0 (0.0)	3 (5.5)	3 (2.7)
Diarrhoea	8 (12.7)	8 (12.9)	6 (10.3)	6 (10.9)	12 (10.6)
Dizziness	5 (7.9)	5 (8.1)	3 (5.2)	1 (1.8)	4 (3.5)
Fall	2 (3.2)	2 (3.2)	1 (1.7)	4 (7.3)	5 (4.4)
Fatigue	2 (3.2)	1 (1.6)	5 (8.6)	3 (5.5)	8 (7.1)
Gastroenteritis	1 (1.6)	0 (0.0)	3 (5.2)	1 (1.8)	4 (3.5)
Gastroenteritis viral	0 (0.0)	2 (3.2)	3 (5.2)	2 (3.6)	5 (4.4)
Headache	12 (19.0)	10 (16.1)	13 (22.4)	6 (10.9)	19 (16.8)
Hypertension	1 (1.6)	2 (3.2)	0 (0.0)	3 (5.5)	3 (2.7)
Influenza	1 (1.6)	1 (1.6)	3 (5.2)	4 (7.3)	7 (6.2)
Insomnia	5 (7.9)	2 (3.2)	0 (0.0)	2 (3.6)	2 (1.8)
Myalgia	2 (3.2)	5 (8.1)	3 (5.2)	2 (3.6)	5 (4.4)
Myasthenia gravis	11 (17.5)	6 (9.7)	4 (6.9)	6 (10.9)	10 (8.8)
Nasopharyngitis	10 (15.9)	9 (14.5)	10 (17.2)	10 (18.2)	20 (17.7)
Nausea	9 (14.3)	8 (12.9)	5 (8.6)	4 (7.3)	9 (8.0)
Neck pain	2 (3.2)	3 (4.8)	2 (3.4)	3 (5.5)	5 (4.4)
Oedema peripheral	2 (3.2)	4 (6.5)	1 (1.7)	2 (3.6)	3 (2.7)
Oral herpes	0 (0.0)	5 (8.1)	0 (0.0)	1 (1.8)	1 (0.9)
Oropharyngeal pain	3 (4.8)	1 (1.6)	4 (6.9)	1 (1.8)	5 (4.4)
Pain in extremity	2 (3.2)	4 (6.5)	4 (6.9)	1 (1.8)	5 (4.4)
Paraesthesia	4 (6.3)	3 (4.8)	0 (0.0)	1 (1.8)	1 (0.9)
Pharyngitis	0 (0.0)	2 (3.2)	0 (0.0)	3 (5.5)	3 (2.7)
Pruritus	4 (6.3)	1 (1.6)	1 (1.7)	1 (1.8)	2 (1.8)
Pyrexia	2 (3.2)	4 (6.5)	1 (1.7)	0 (0.0)	1 (0.9)
Upper respiratory tract infection	12 (19.0)	10 (16.1)	3 (5.2)	2 (3.6)	5 (4.4)
Urinary tract infection	5 (7.9)	4 (6.5)	0 (0.0)	1 (1.8)	1 (0.9)
Vomiting	5 (7.9)	3 (4.8)	2 (3.4)	2 (3.6)	4 (3.5)

Notes: TEAEs were AEs with a start date on or after the date of the first study drug dose. If a patient had more than one TEAE for a particular SOC, he/she is counted only once for that SOC. If a patient had more than one TEAE for a particular preferred term, he/she was counted only once for that preferred term. Patient percentages were based on the total number of patients in the Safety Set in the particular treatment arm or overall.
Abbreviations: AE = adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event

Table 41 Treatment-Emergent Adverse Events by Preferred Term in Study C08-001 (Events Occurring in ≥3 Patients) – Safety Population

Preferred Term	Placebo (N = 13) n (%)	Eculizumab (N = 13) n (%)
Back pain	1 (7.7)	4 (30.8)
Cough	0 (0.0)	3 (23.1)
Headache	4 (30.8)	3 (23.1)
Myalgia	2 (15.4)	3 (23.1)
Nasopharyngitis	2 (15.4)	3 (23.1)
Nausea	2 (15.4)	4 (30.8)
Neck pain	1 (7.7)	3 (23.1)

- **Adverse Events by Relationship to Study Drug**

In Study ECU-MG-301, 55 (44.0%) patients overall (30 [48.4%] patients in the eculizumab arm and 25 [39.7%] patients in the placebo arm) reported AEs that were considered related to the study drug.

In patients treated with eculizumab, the incidence of not related headaches (7 [11.3%] patients) was higher than related headaches (3 [4.8%] patients), while the incidence of not related and related headaches was similar in patients treated with placebo (6 [9.5%] patients with not related headache and 7 [11.1%] patients with related headache). The incidence of related nausea was higher than not related nausea in both treatment arms (5 [8.1%] patients versus 3 [4.8%] patients in the eculizumab arm; 7 [11.1%] patients versus 2 [3.2%] patients in the placebo arm). In the placebo arm, more patients had not related events of diarrhoea (5 [7.9% patients) than related events (3 [4.8%] patients), while the opposite was observed in the eculizumab arm (3 [4.8%] patients with not related diarrhoea and 6 [9.7%] patients with related diarrhoea). While upper respiratory infection, MG, nasopharyngitis, and back pain were relatively frequently reported AEs, these events were considered not related to the study drug in the majority of patients in both treatment arms.

In Study ECU-MG-302, 37 (32.7%) patients overall (19 [32.8%] patients in the placebo/eculizumab arm and 18 [32.7%] patients in the eculizumab/eculizumab arm) reported AEs that were considered related to the study drug. The AEs most commonly considered to be related to the study drug were headache (related in 7 [6.2%] patients overall; not related in 12 [10.6%] patients overall) and diarrhoea (related in 7 [6.2%] patients overall; not related in 5 [4.4%] patients overall).

In Study C08-001 related events of nausea and headache were each experienced by 3 (23.1%) patients during treatment with eculizumab. Related events of neck pain and myalgia were each experienced by 2 (15.4%) patients during treatment with eculizumab.

Table 42 Treatment-Emergent Adverse Events by Preferred Term, Grouped Relationship to Study Drug, and Treatment Arm in Studies ECU-MG-301 and ECU-MG-302 Side-by-Side (Events Occurring in ≥5% of Patients in Either Treatment Arm in Either Study) – Safety Set

	Study ECU-MG-301				Study ECU-MG-302					
	Placebo N = 63		Eculizumab N = 62		Placebo/ Eculizumab N = 58		Eculizumab/ Eculizumab N = 55		Total N = 113	
Preferred Term	Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)
Patients with events	25 (39.7)	55 (87.3)	30 (48.4)	49 (79.0)	19 (32.8)	38 (65.5)	18 (32.7)	30 (54.5)	37 (32.7)	68 (60.2)
Arthralgia	1 (1.6)	3 (4.8)	0 (0.0)	1 (1.6)	0 (0.0)	2 (3.4)	1 (1.8)	2 (3.6)	1 (0.9)	4 (3.5)
Back pain	0 (0.0)	6 (9.5)	0 (0.0)	5 (8.1)	0 (0.0)	3 (5.2)	1 (1.8)	1 (1.8)	1 (0.9)	4 (3.5)
Chills	3 (4.8)	1 (1.6)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Contusion	1 (1.6)	1 (1.6)	3 (4.8)	3 (4.8)	0 (0.0)	2 (3.4)	2 (3.6)	2 (3.6)	2 (1.8)	4 (3.5)
Cough	0 (0.0)	3 (4.8)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	2 (3.6)	2 (1.8)	2 (1.8)
Diarrhoea	3 (4.8)	5 (7.9)	6 (9.7)	3 (4.8)	3 (5.2)	3 (5.2)	4 (7.3)	2 (3.6)	7 (6.2)	5 (4.4)
Dizziness	2 (3.2)	3 (4.8)	3 (4.8)	2 (3.2)	3 (5.2)	0 (0.0)	0 (0.0)	1 (1.8)	3 (2.7)	1 (0.9)
Fall	0 (0.0)	2 (3.2)	0 (0.0)	2 (3.2)	0 (0.0)	1 (1.7)	0 (0.0)	4 (7.3)	0 (0.0)	5 (4.4)
Fatigue	1 (1.6)	1 (1.6)	1 (1.6)	0 (0.0)	3 (5.2)	2 (3.4)	0 (0.0)	3 (5.5)	3 (2.7)	5 (4.4)
Gastroenteritis	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	2 (3.4)	1 (1.7)	0 (0.0)	1 (1.8)	2 (1.8)	2 (1.8)
Gastroenteritis viral	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	3 (5.2)	1 (1.8)	1 (1.8)	1 (0.9)	4 (3.5)
Headache	7 (11.1)	6 (9.5)	3 (4.8)	7 (11.3)	4 (6.9)	9 (15.5)	3 (5.5)	3 (5.5)	7 (6.2)	12 (10.6)
Hypertension	0 (0.0)	1 (1.6)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.8)	2 (3.6)	1 (0.9)	2 (1.8)
Influenza	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	3 (5.2)	1 (1.8)	3 (5.5)	1 (0.9)	6 (5.3)
Insomnia	0 (0.0)	5 (7.9)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)	2 (1.8)
Myalgia	2 (3.2)	0 (0.0)	1 (1.6)	4 (6.5)	1 (1.7)	2 (3.4)	2 (3.6)	0 (0.0)	3 (2.7)	2 (1.8)
Myasthenia gravis	0 (0.0)	11 (17.5)	1 (1.6)	5 (8.1)	1 (1.7)	3 (5.2)	1 (1.8)	5 (9.1)	2 (1.8)	8 (7.1)
Nasopharyngitis	1 (1.6)	9 (14.3)	3 (4.8)	6 (9.7)	1 (1.7)	9 (15.5)	3 (5.5)	7 (12.7)	4 (3.5)	16 (14.2)
Nausea	7 (11.1)	2 (3.2)	5 (8.1)	3 (4.8)	2 (3.4)	3 (5.2)	0 (0.0)	4 (7.3)	2 (1.8)	7 (6.2)
Neck pain	0 (0.0)	2 (3.2)	0 (0.0)	3 (4.8)	0 (0.0)	2 (3.4)	2 (3.6)	1 (1.8)	2 (1.8)	3 (2.7)
Oedema peripheral	1 (1.6)	1 (1.6)	1 (1.6)	3 (4.8)	0 (0.0)	1 (1.7)	1 (1.8)	1 (1.8)	1 (0.9)	2 (1.8)
Oral herpes	0 (0.0)	0 (0.0)	4 (6.5)	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)
Oropharyngeal pain	0 (0.0)	3 (4.8)	0 (0.0)	1 (1.6)	1 (1.7)	4 (6.9)	0 (0.0)	1 (1.8)	1 (0.9)	5 (4.4)
Pain in extremity	0 (0.0)	2 (3.2)	0 (0.0)	4 (6.5)	0 (0.0)	4 (6.9)	1 (1.8)	1 (1.8)	1 (0.9)	5 (4.4)
Paraesthesia	1 (1.6)	3 (4.8)	0 (0.0)	3 (4.8)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.5)	0 (0.0)	3 (2.7)
Pruritus	1 (1.6)	4 (6.3)	1 (1.6)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.8)	0 (0.0)	2 (1.8)	0 (0.0)
Pyrexia	0 (0.0)	2 (3.2)	2 (3.2)	2 (3.2)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Upper respiratory tract infection	2 (3.2)	10 (15.9)	3 (4.8)	8 (12.9)	0 (0.0)	3 (5.2)	0 (0.0)	2 (3.6)	0 (0.0)	5 (4.4)
Urinary tract infection	2 (3.2)	3 (4.8)	1 (1.6)	3 (4.8)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)
Vomiting	2 (3.2)	3 (4.8)	0 (0.0)	3 (4.8)	1 (1.7)	1 (1.7)	0 (0.0)	2 (3.6)	1 (0.9)	3 (2.7)

Notes: Related AEs are defined as AEs that are possibly, probably, or definitely related to the study drug. Not relatedAEs are defined as AEs that are not related or unlikely to be related to the study drug.
Abbreviations: AE = adverse event

Table 43 Treatment-Emergent Adverse Events by Preferred Term and Relationship to Study Drug (Events Occurring in ≥3 Patients) in Study C08-001 – Safety Population

Preferred Term	Placebo (N = 13)		Eculizumab (N = 13)	
	Related n (%)	Not Related n (%)	Related n (%)	Not Related n (%)
Back pain	1 (7.7)	0 (0.0)	2 (15.4)	2 (15.4)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	3 (23.1)
Headache	2 (15.4)	2 (15.4)	3 (23.1)	0 (0.0)
Myalgia	1 (7.7)	1 (7.7)	2 (15.4)	1 (7.7)
Nasopharyngitis	0 (0.0)	2 (15.4)	0 (0.0)	3 (23.1)
Nausea	1 (7.7)	1 (7.7)	3 (23.1)	1 (7.7)
Neck pain	0 (0.0)	1 (7.7)	0 (0.0)	3 (23.1)

Notes: Related AEs are defined as AEs that are possibly, probably, or definitely related to the study drug. Not related AEs are defined as AEs that are not related or unlikely to be related to the study drug.
Abbreviations: AE = adverse event

- **Adverse Events by Severity**

In Study ECU-MG-301, the majority of events reported in both treatment arms were of mild or moderate severity. One or more severe AEs were experienced by 8 (12.9%) patients in the eculizumab arm and 16 (25.4%) patients in the placebo arm. Excluding the events related to MG deterioration, more severe AEs were reported overall in the SOC of Infections and Infestations (eculizumab: 2 [3.2%] patients; placebo: 4 [6.3%] patients) than in any other SOC. In the eculizumab arm, the severe AEs in the SOC of Infections and Infestations included bacteraemia, diverticulitis, and endocarditis (each reported as severe by 1 [0.8%] patient). Other severe AEs that occurred in patients treated with eculizumab include MG (4 [6.5%] patients) and lymphopenia, intestinal perforation, pyrexia, post-procedural fistula, decreased weight, critical illness myopathy, myalgia, MG crisis, and atelectasis (1 [1.6%] patient each).

The majority of events reported in both treatment arms in Study ECU-MG-302 were of mild or moderate severity. One or more severe AEs were experienced by 6 (10.3%) patients in the placebo/eculizumab arm and 9 (16.4%) patients in the eculizumab/eculizumab arm. The only AEs considered severe in more than 1 patient in Study ECU-MG-302 were MG (4 patients overall experiencing severe MG) and diarrhoea (2 patients overall experiencing severe diarrhoea).

Treatment-emergent AEs that occurred in ≥3 patients in Study C08-001 are summarized by severity in Table 16. Other AEs that were reported as severe by at least one patient include the following:

- Carpal tunnel syndrome (n = 1 [severe] in the placebo arm; n = 0 in the eculizumab arm)
- Cellulitis (n = 1 [severe] in the placebo arm; n = 0 in the eculizumab arm)
- Erectile dysfunction (n = 0 in the placebo arm; n = 1 [severe] in the eculizumab arm)
- MG (n = 0 in the placebo arm; n = 1 [severe] in the eculizumab arm)
- MG crisis (n = 1 [severe] in the placebo arm; n = 0 in the eculizumab arm)
- Nephrolithiasis (n = 0 in the placebo arm; n = 1 [severe] in the eculizumab arm)
- Tendon rupture (n = 0 in the placebo arm; n = 1 [severe] in the eculizumab arm)

Table 44 Treatment-Emergent Adverse Events by Preferred Term, Severity, and Treatment Arm in Studies ECU-MG-301 and ECU-MG-302

	Study ECU-MG-301						Study ECU-MG-302								
	Placebo N = 63			Eculizumab N = 62			Placebo/ Eculizumab N = 58			Eculizumab/ Eculizumab N = 55			Total N = 113		
Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Patients with events	52 (82.5)	34 (54.0)	16 (25.4)	49 (79.0)	26 (41.9)	8 (12.9)	40 (69.0)	17 (29.3)	6 (10.3)	34 (61.8)	19 (34.5)	9 (16.4)	74 (65.5)	36 (31.9)	15 (13.3)
Arthralgia	3 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	2 (3.6)	1 (1.8)	0 (0.0)	2 (1.8)	3 (2.7)	0 (0.0)
Back pain	3 (4.8)	3 (4.8)	0 (0.0)	4 (6.5)	2 (3.2)	0 (0.0)	2 (3.4)	1 (1.7)	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	4 (3.5)	1 (0.9)	0 (0.0)
Chills	3 (4.8)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Contusion	2 (3.2)	0 (0.0)	0 (0.0)	4 (6.5)	2 (3.2)	0 (0.0)	2 (3.4)	0 (0.0)	0 (0.0)	3 (5.5)	0 (0.0)	1 (1.8)	5 (4.4)	0 (0.0)	1 (0.9)
Cough	2 (3.2)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	1 (1.8)	0 (0.0)	2 (1.8)	1 (0.9)	0 (0.0)
Diarrhoea	6 (9.5)	1 (1.6)	1 (1.6)	7 (11.3)	1 (1.6)	0 (0.0)	5 (8.6)	1 (1.7)	0 (0.0)	5 (9.1)	1 (1.8)	2 (3.6)	10 (8.8)	2 (1.8)	2 (1.8)
Dizziness	3 (4.8)	3 (4.8)	0 (0.0)	3 (4.8)	2 (3.2)	0 (0.0)	3 (5.2)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	4 (3.5)	0 (0.0)	0 (0.0)
Fall	1 (1.6)	1 (1.6)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	4 (7.3)	0 (0.0)	0 (0.0)	4 (3.5)	1 (0.9)	0 (0.0)
Fatigue	1 (1.6)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	3 (5.2)	2 (3.4)	1 (1.7)	3 (5.5)	0 (0.0)	0 (0.0)	6 (5.3)	2 (1.8)	1 (0.9)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.8)	0 (0.0)	2 (1.8)	1 (0.9)	1 (0.9)
Gastroenteritis viral	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)	0 (0.0)	2 (3.4)	1 (1.7)	0 (0.0)	1 (1.8)	1 (1.8)	0 (0.0)	3 (2.7)	2 (1.8)	0 (0.0)
Headache	8 (12.7)	5 (7.9)	1 (1.6)	9 (14.5)	1 (1.6)	0 (0.0)	11 (19.0)	4 (6.9)	1 (1.7)	6 (10.9)	1 (1.8)	0 (0.0)	17 (15.0)	5 (4.4)	1 (0.9)
Hypertension	1 (1.6)	0 (0.0)	0 (0.0)	2 (3.2)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.5)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)	0 (0.0)
Influenza	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	2 (3.4)	1 (1.7)	0 (0.0)	3 (5.5)	2 (3.6)	0 (0.0)	5 (4.4)	3 (2.7)	0 (0.0)
Insomnia	4 (6.3)	1 (1.6)	0 (0.0)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Myalgia	2 (3.2)	0 (0.0)	0 (0.0)	4 (6.5)	1 (1.6)	1 (1.6)	3 (5.2)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	5 (4.4)	0 (0.0)	0 (0.0)
Myasthenia gravis	0 (0.0)	7 (11.1)	5 (7.9)	1 (1.6)	1 (1.6)	4 (6.5)	1 (1.7)	1 (1.7)	2 (3.4)	1 (1.8)	4 (7.3)	2 (3.6)	2 (1.8)	5 (4.4)	4 (3.5)
Nasopharyngitis	9 (14.3)	1 (1.6)	0 (0.0)	8 (12.9)	2 (3.2)	0 (0.0)	10 (17.2)	0 (0.0)	0 (0.0)	9 (16.4)	1 (1.8)	0 (0.0)	19 (16.8)	1 (0.9)	0 (0.0)
Nausea	9 (14.3)	1 (1.6)	0 (0.0)	5 (8.1)	3 (4.8)	0 (0.0)	4 (6.9)	2 (3.4)	1 (1.7)	4 (7.3)	0 (0.0)	0 (0.0)	8 (7.1)	2 (1.8)	1 (0.9)
Neck pain	0 (0.0)	2 (3.2)	0 (0.0)	2 (3.2)	1 (1.6)	0 (0.0)	2 (3.4)	0 (0.0)	0 (0.0)	2 (3.6)	1 (1.8)	0 (0.0)	4 (3.5)	1 (0.9)	0 (0.0)
Oedema peripheral	1 (1.6)	1 (1.6)	0 (0.0)	4 (6.5)	1 (1.6)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.8)	1 (1.8)	0 (0.0)	2 (1.8)	1 (0.9)	0 (0.0)
Oral herpes	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Oropharyngeal pain	3 (4.8)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	4 (6.9)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	5 (4.4)	0 (0.0)	0 (0.0)
Pain in extremity	1 (1.6)	1 (1.6)	0 (0.0)	3 (4.8)	1 (1.6)	0 (0.0)	3 (5.2)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	3 (2.7)	2 (1.8)	0 (0.0)
Paraesthesia	4 (6.3)	0 (0.0)	0 (0.0)	2 (3.2)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.9)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.5)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)	0 (0.0)
Pruritus	3 (4.8)	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Pyrexia	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.8)	1 (1.6)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	7 (11.1)	5 (7.9)	1 (1.6)	9 (14.5)	2 (3.2)	0 (0.0)	2 (3.4)	1 (1.7)	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	4 (3.5)	1 (0.9)	0 (0.0)
Urinary tract infection	4 (6.3)	1 (1.6)	0 (0.0)	4 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Vomiting	5 (7.9)	0 (0.0)	0 (0.0)	3 (4.8)	1 (1.6)	0 (0.0)	1 (1.7)	1 (1.7)	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	3 (2.7)	1 (0.9)	0 (0.0)

Table 45: Treatment-Emergent Adverse Events by Preferred Term and Severity in Study C08-001 (Events Occurring in ≥3 Patients) – Safety Population

Preferred Term	Placebo (N = 13)			Eculizumab (N = 13)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Back pain	0 (0.0)	0 (0.0)	1 (7.7)	2 (15.4)	2 (15.4)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	2 (15.4)	1 (7.7)	0 (0.0)
Headache	3 (23.1)	1 (7.7)	0 (0.0)	2 (15.4)	1 (7.7)	0 (0.0)
Myalgia	1 (7.7)	1 (7.7)	0 (0.0)	2 (15.4)	1 (7.7)	0 (0.0)
Nasopharyngitis	2 (15.4)	0 (0.0)	0 (0.0)	2 (15.4)	1 (7.7)	0 (0.0)
Nausea	0 (0.0)	2 (15.4)	0 (0.0)	3 (23.1)	1 (7.7)	0 (0.0)
Neck pain	1 (7.7)	0 (0.0)	0 (0.0)	1 (7.7)	2 (15.4)	0 (0.0)

Serious adverse event / deaths / other significant events

- **Deaths**

Two patients who were treated with eculizumab as part of this clinical program have died.

One patient who had been treated in Study ECU-MG-301 subsequently died. This patient, a 73-year-old, white female in the eculizumab arm, discontinued from the study on Study Day 128 due to MG crisis. The patient was hospitalized on Study Day 112 due to worsening of her MG symptoms. She underwent plasmapheresis 5 times over the course of 12 days (Study Days 113 through 124), with a supplemental dose of the study drug following 4 of the 5 plasmapheresis treatments. The patient remained hospitalized and, on Study Day 127, was transferred to the hospital intensive care unit (ICU) due to onset of MG crisis. She received several treatments with IVIg while in the ICU, and experienced additional AEs during

hospitalization. While the patient recovered from the events of pneumonia, sepsis, and Clostridium difficile infection, the events of atelectasis, post-procedural fistula, and critical illness myopathy were ongoing at the time of her death on 20 Feb 2016 (89 days after her last dose of study drug). At the time of these events, the patient was receiving the following concomitant medications: alprazolam, citalopram, famotidine, human mixtard, insulin human, MMF, pantoprazole, sodium sesquihydrate, potassium chloride, pyridostigmine, sucralfate, and salbutamol sulfate. The Investigator considered the events of MG and MG crisis to be possibly related to eculizumab.

One patient in Study ECU-MG-302 died after the date on which data from the clinical database were extracted for this interim analysis. Thus, data for this patient are preliminary. This patient, a 25-year-old white female in the eculizumab/eculizumab arm, was hospitalized on 14 Apr 2016 (Study Day 81) with pyrexia, developed sepsis, and died on 29 Apr 2016 (Study Day 96) with cause of death reported as multi-organ failure.

The Investigator considered the event of disseminated intravascular coagulation (DIC) as unlikely to be related to eculizumab. Pyrexia and hepatic failure were considered as possibly related to eculizumab, and both sepsis and cytomegalovirus (CMV) infection were considered by the Investigator to be probably related to eculizumab. However, this patient's chronic immunosuppression secondary to use of steroids and azathioprine (risk factors for CMV, viral and bacterial infections), along with increasing doses of steroids immediately prior to onset of this febrile syndrome, likely contributed to her clinical picture. A definitive diagnosis of CMV infection is difficult given the absence of post mortem biopsies showing inclusion bodies, and only a qualitative test of CMV antigen without quantitation. Moreover, nosocomial pneumonia secondary to multi-drug resistant Acinetobacter baumanni (a nosocomial infection) cannot be ruled out as a major contributing factor to the progressive syndrome of hypotension, respiratory failure, DIC, and multi-organ failure. The relationship of the clinical syndrome and related events to eculizumab are in the opinion of the Sponsor, difficult to ascertain, given the complexity of the clinical picture and multiple confounding factors.

No patients died during the Study C08-001.

- **Serious Adverse Events**

Of the 125 patients in the Safety Set of Study ECU-MG-301, 27 (21.6%) reported a total of 50 SAEs (17 in the eculizumab arm and 33 in the placebo arm). The number (percentage) of patients reporting one or more SAEs was 9 (14.5%) in the eculizumab arm and 18 (28.6%) in the placebo arm. The most common SAE was MG, which was reported in 5 (8.1%) patients in the eculizumab arm and 8 (12.7%) patients in the placebo arm. The only other preferred terms with more than 2 reported SAEs overall were pyrexia (2 [3.2%] patients in the eculizumab arm and no patients in the placebo arm) and upper respiratory tract infection (no patients in the eculizumab arm and 2 [3.2%] patients in the placebo arm).

In Study ECU-MG-302, SAEs were experienced by 9 (15.5%) patients in the placebo/eculizumab arm and 9 (16.4%) patients in the eculizumab/eculizumab arm. Similar to Study ECU-MG-301, the most common SAE was MG, which was reported in 3 (5.2%) patients in the placebo/eculizumab arm and 4 (7.3%) patients in the eculizumab/eculizumab arm. The only other preferred term with at least 2 reported SAEs overall was influenza (no patients in the placebo/eculizumab arm and 2 (3.6%) patients in the eculizumab/eculizumab arm). While SAEs of pyrexia and upper respiratory tract infection were observed in Study ECU-MG-301, these SAEs did not occur in any patient in Study ECU-MG-302 up to 01 Mar 2016 (the clinical database cut-off date for this interim analysis).

Consistent with these findings, there were 27 patients with hospitalizations in Study ECU-MG-301 (18 [28.6%] patients in the placebo arm, and 9 [14.5%] patients in the eculizumab arm). In Study ECU-MG-302, a total of 18 (15.9%) patients reported hospitalization.

In Study C08-001 one patient experienced 2 SAEs following cross-over from eculizumab, namely MG exacerbation and MG crisis, during the Wash-Out Period and Treatment Period 2 (placebo), respectively.

Table 45 Treatment Emergent Serious Adverse Events by Preferred Term and Treatment Arm in Studies ECU-MG-301 and ECU-MG-302 Side-by-Side – Safety Set

	Study ECU-MG-301		Study ECU-MG-302		
	Placebo N = 63	Eculizumab N = 62	Placebo/ Eculizumab N = 58	Eculizumab/ Eculizumab N = 55	Total N = 113
Patient Years of Exposure	31.1	29.6	24.9	22.2	47.1
Preferred Term, n (%)					
Patients with TESAEs	18 (28.6)	9 (14.5)	9 (15.5)	9 (16.4)	18 (15.9)
Acute kidney injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
Apnoea	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bacteraemia	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis acute	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deep vein thrombosis	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diverticulitis	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Endocarditis	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Gastritis	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	1 (1.6)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.9)
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
General physical health deterioration	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.9)
Hyperglycaemia	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	2 (1.8)
Intentional overdose	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intestinal obstruction	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
Intestinal perforation	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Loss of consciousness	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.9)
Lymphocyte count decreased	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphopenia	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant melanoma in situ	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.9)
Metastases to bone	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Myasthenia gravis	8 (12.7)	5 (8.1)	3 (5.2)	4 (7.3)	7 (6.2)
Myasthenia gravis crisis	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.8)	1 (0.9)
Ovarian cyst	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
Prostate cancer	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Pseudomonal sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
Pulmonary embolism	1 (1.6)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.9)
Pyrexia	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory syncytial virus infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
Small intestinal obstruction	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
Syncope	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.9)
Tonsillitis	1 (1.6)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.9)
Upper respiratory tract infection	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection bacterial	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Varicella	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Notes: TESAEs are SAEs with a start date on or after the first dose date in the study. If a patient had more than one TESAE for a particular SOC, he/she is counted only once for that SOC. If a patient had more than one TESAE for a particular Preferred Term, he/she is counted only once for that Preferred Term. Patient percentages are based on the total number of patients in the Safety Set in the particular treatment arm or overall.
Abbreviations: SAEs = serious adverse events; SOC = System Organ Class; TESAEs = treatment-emergent serious adverse events

Adverse events of Special interest

In Study ECU-MG-301, a total of 6 AESIs were reported by 4 (6.5%) patients in the eculizumab arm, and a total of 19 AESIs were reported by 11 (17.5%) patients in the placebo arm. The most frequently reported AESIs by SOC were Infections and Infestations, followed by General Disorders and Administration Site Conditions. A total of 5 events in the SOC of Infections and Infestations were reported by 3 (4.8%) patients in the eculizumab arm; 7 events were reported by 6 (9.5%) patients in the placebo arm.

In Study ECU-MG-302, a total of 30 AESIs were reported by 15 (13.3%) patients. Adverse events of special interest were most commonly experienced in the SOC of Infections and Infestations (6 [5.3%] patients overall).

None of the patients included in this clinical program have developed *N. meningitidis* infection.

Serious AESIs occurred only in the SOC of Infections and Infestations during Studies ECU-MG-301 and ECU-MG-302. In Study ECU-MG-301, 7 events were experienced by 6 (9.5%) patients in the placebo arm, and 4 events were experienced by 2 (3.2%) patients in the eculizumab arm. The only serious AESI to occur in more than 1 patient was upper respiratory tract infection, which was experienced by 2 patients in the placebo arm and no patients in the eculizumab arm. In Study ECU-MG-302, a total of 7 events were experienced by 6 (5.3%) patients overall.

Adverse events of special interest were not prospectively defined or presented for Study C08-001. However, imposing the definition for AESIs developed during Studies ECU-MG-301 and ECU-MG-302, none of the AEs that occurred in Study C08-001 met the criteria for AESI.

Table 46 Treatment-Emergent Serious Adverse Events of Special Interest by Medical Dictionary for Regulatory Activities System Organ Class / Preferred Term by Treatment Arm in Study ECU-MG-301 – Safety Set

	Study ECU-MG-301				Study ECU-MG-302					
	Placebo (N = 63)		Eculizumab (N = 62)		Placebo/Eculizumab (N = 58)		Eculizumab/Eculizumab (N = 55)		Total (N = 113)	
Patient Years of Exposure	31.1		29.6		24.9		22.2		47.1	
System Organ Class Preferred term	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Events and Patients with Events	7	6 (9.5)	4	2 (3.2)	2	2 (3.4)	5	4 (7.3)	7	6 (5.3)
Infections and infestations	7	6 (9.5)	4	2 (3.2)	2	2 (3.4)	5	4 (7.3)	7	6 (5.3)
Bacteraemia	0	0 (0.0)	1	1 (1.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Diverticulitis	0	0 (0.0)	2	1 (1.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Endocarditis	0	0 (0.0)	1	1 (1.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Gastroenteritis	2	1 (1.6)	0	0 (0.0)	1	1 (1.7)	0	0 (0.0)	1	1 (0.9)
Influenza	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (3.6)	2	2 (1.8)
Pneumonia	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (1.8)	1	1 (0.9)
Pseudomonal sepsis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (1.8)	1	1 (0.9)
Respiratory syncytial virus infection	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (1.8)	1	1 (0.9)
Tonsillitis	1	1 (1.6)	0	0 (0.0)	1	1 (1.7)	0	0 (0.0)	1	1 (0.9)
Upper respiratory tract infection	2	2 (3.2)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Urinary tract infection bacterial	1	1 (1.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Varicella	1	1 (1.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

Laboratory findings

Haematology:

No clinically significant differences in haematology parameters were observed comparing placebo and eculizumab treatment.

The most common clinically significant abnormality in haematology parameters was related to abnormally low lymphocytes (AEs of lymphopenia or lymphocyte count decreased). However, these abnormalities were experienced by patients in both treatment arms in Study ECU-MG-301, and most of the events in both studies were considered not related to the study drug. These data suggest that eculizumab does not have a clinically meaningful impact on haematology parameters.

Chemistry

Of the 133 patients treated with eculizumab, only 5 patients experienced a clinically significant abnormality in a chemistry parameter, and none of the events were serious. While the relationship to the study drug could not be excluded for several of these events, an additional 3 patients experienced clinically significant chemistry abnormalities while being treated with placebo in Study ECU-MG-301. These data suggest that eculizumab does not have a clinically meaningful impact on chemistry parameters.

Vital Sign Measurements and Other Physical Findings

Results from the 3 studies in this clinical development program do not suggest any impact of eculizumab on vital signs or other physical findings.

Electrocardiograms

Across studies, there were no findings to suggest that eculizumab impacts cardiac function. Only 2 of the 133 patients treated with eculizumab experienced a clinically significant abnormal electrocardiogram finding, neither of which impacted the patient's ability to continue treatment with eculizumab.

Columbia Suicide Severity Rating Scale

The single patient in the eculizumab arm who experienced suicidal behaviour during Study ECU-MG-301 had no suicidal ideation or behaviour in Study ECU-MG-302, while one patient experienced suicidal ideation in the extension study after not having experienced such in Study ECU-MG-301. One patient in the placebo arm who had no suicidal ideation or behaviour during Study ECU-MG-301 experienced suicidal ideation in Study ECU-MG-302. Four patients in the placebo arm who experienced suicidal ideation or behaviour during Study ECU-MG-301 no longer experienced such after switching to eculizumab in Study ECU-MG-302.

Overall, results from Studies ECU-MG-301 and ECU-MG-302 suggest that treatment with eculizumab does not put patients at increased risk for suicidal ideation or behaviour and might reduce suicidal ideation and behaviour in this patient population, possibly due to an improvement in underlying gMG morbidity.

Immunogenicity

Blood samples for human ADA analysis for IgG and IgM were collected to describe the presence or absence of an immune response to eculizumab and to evaluate, if antibodies were detected, whether the antibodies neutralise the activity of eculizumab (ie, the ability of eculizumab to inhibit C5 cleavage by C5 convertase).

Results from Study ECU-MG-301 indicate that treatment with eculizumab over 26 weeks does not lead to the production of ADA. The results from this study are supported by results from Studies ECU-MG-302 and C08-001.

Safety in special populations

- **Intrinsic Factors**

Age

Of the 125 patients randomized in Study ECU-MG-301, 102 (81.6%) were between the ages of 18 and 65; 23 (18.4%) were >65 years of age.

In the placebo arm in Study ECU-MG-301, 18 (35.3%) patients of age 18 to 65 years experienced one or more study drug-related AEs, while 7 (58.3%) patients of age >65 years experienced one or more study drug-related AEs. The number of patients experiencing a study drug-related AE in the eculizumab arm was 24 (47.1%) patients of age 18 to 65 years and 6 (54.5%) patients of age >65 years.

In the placebo arm, younger patients had a higher incidence of SAEs (16 [31.4%] patients of age 18 to 65 years, and 2 [16.7%] patients of age >65 years) while, in the eculizumab arm, younger patients had a lower incidence of SAEs (6 [11.8%] patients of age 18 to 65 years, and 3 [27.3%] patients of age >65 years).

Gender

Of the 125 patients randomized in Study ECU-MG-301, 43 (34.4%) were male and 82 (65.6%) were female. A similar proportion of males and females experienced one or more AEs in both treatment groups. Similarly, there was no difference across genders in the proportion of patients with one or more study drug-related AEs.

While a similar proportion of males and females in the placebo arm experienced one or more SAEs, a greater proportion of males (6 [28.6%] patients) experienced one or more SAEs than females (3 [7.3%] patients) on eculizumab. SAEs leading to discontinuation were reported in 2 male patients (9.5%) treated with eculizumab and 2 female patients (4.9%) treated with eculizumab. There were no placebo patients with SAEs leading to discontinuation.

Race

Of the 125 patients randomized in Study ECU-MG-301, 95 (76.0%) were white, 19 (15.2%) were Asian, 3 (2.4%) were black or African American, and 8 (6.4%) were of other race. Based on the limited number of patients enrolled in some race categories in one or both treatment arms, no clinically meaningful comparisons can be made based on race for AEs, SAEs, and study drug-related AEs.

Geographic Region

Of the 125 patients randomized in Study ECU-MG-301, 51 (40.8%) were from Europe, 46 (36.8%) were from North America, 12 (9.6%) were from South America, 11 (8.8%) were from Japan, and 5 (4.0%) were from the Asia-Pacific (Korea).

Of patients treated with eculizumab, a lesser proportion of patients from Europe (78.8%) experienced one or more AEs than patients from North America (100.0%). However, eculizumab-treated patients from Europe experienced more SAEs than patients from North America, but less SAEs than placebo patients from Europe. Of the 4 patients who had AEs that led to discontinuation of eculizumab, 3 were from Europe and 1 was from North America. While a limited number of patients were enrolled from South America, Asia-Pacific, and Japan in one or both treatment arms, available data do not suggest differences in TEAEs in these geographic regions compared to the population overall.

- **Extrinsic Factors**

Safety analyses by extrinsic factors were not performed.

Safety related to drug-drug interactions and other interactions

Drug interactions were not studied in Studies C08-001, ECU-MG-301, or ECU-MG-302.

Discontinuation due to adverse events

In Study ECU-MG-301, 7 patients who were treated with either placebo or eculizumab discontinued from the study (Table 45): 5 in the eculizumab arm and 2 in the placebo arm. In the eculizumab arm, 4 discontinuations were due to AEs, and 1 patient withdrew consent.

Two patients in the placebo arm withdrew consent. Within the week prior to their withdrawal, both of these patients were hospitalized for MG deterioration.

As of the clinical database cut-off date (01 Mar 2016), 7 patients had discontinued from Study ECU-MG-302: 5 in the eculizumab/eculizumab arm and 2 in the placebo/eculizumab arm (Table 47). One patient discontinued due to an AE, and this patient was in the eculizumab/eculizumab arm.

Two patients from the placebo/eculizumab arm withdrew consent. Both of these patients were experiencing 1 or more AEs at the time of withdrawing consent; however, the reason for withdrawal was not considered due to an AE.

Patients in Study C08-001 who were treated with eculizumab during Period 1 discontinued eculizumab as specified by the crossover study design, followed by a Wash-out Period and treatment with placebo in Period 2.

Table 47 Discontinuations from Study ECU-MG-301 and Study ECU-MG-302

Study Day of Discontinuation[a]	Reason for Discontinuation	Treatment Arm
80 (80/32)	SAE (Bacteraemia)	Eculizumab
127 (127/99)	SAE (Intestinal perforation)	Eculizumab
128 (128/126)	SAE (MG; Myasthenic crisis)	Eculizumab
85 (85/70)	SAE (Prostate cancer; Metastases to bone)	Eculizumab
37 (37/22)	Patient withdrew consent citing failure to improve to her satisfaction	Eculizumab
28 (28/0)	Patient withdrew consent	Placebo
71 (71/0)	Patient withdrew consent	Placebo
192 (387/324)	SAE (MG)	Eculizumab/Eculizumab
108 (300/286)	Patient withdrew consent	Eculizumab/Eculizumab
161 (356/343)	Other	Eculizumab/Eculizumab
62 (258/197)	Patient withdrew consent	Eculizumab/Eculizumab
183 (379/379)	Physician decision	Eculizumab/Eculizumab
113 (309/99)	Patient withdrew consent	Placebo/Eculizumab
154 (359/125)	Patient withdrew consent	Placebo/Eculizumab

a Study Day is depicted as Study Day of Current Study (Study Day of ECU-MG-301 + ECU-MG-302/Days of Treatment with Eculizumab)
Abbreviations: MG = myasthenia gravis; SAE = serious adverse event

Use in Pregnancy and Lactation

No pregnant or breastfeeding patients were enrolled in Studies C08-001, ECU-MG-301, or ECU-MG-302.

There have been no additional preclinical in vivo studies examining eculizumab in pregnancy conducted since the original eculizumab biologics license application was filed in 2006.

Overdose and Drug Abuse

No cases of eculizumab overdose have been reported during clinical studies.

The potential for drug abuse was not investigated or reported in human clinical studies of eculizumab.

Withdrawal and Rebound

The potential for drug abuse was not investigated or reported in human clinical studies of eculizumab. However, based on the pharmacological profile of eculizumab and the available postmarketing data, there is no evidence of abuse or dependency.

Use of Soliris in refractory gMG treatment has been studied in the setting of chronic administration. Study observations indicate that discontinuation of eculizumab in a disease characterized by unremitting

uncontrolled terminal complement activation exposes patients to the risk of substantial disease worsening as demonstrated by worsened QMG and MG-ADL score in Study C08-001 in patients who stopped eculizumab treatment.

Due to the crossover design of Study C08-001, 7 patients who were treated with eculizumab were then to be treated with placebo after a 5-week wash-out period. All 7 patients treated with eculizumab in Period 1 completed that period. Out of these 7 patients, 6 patients then switched to placebo treatment in Period 2. After completing Period 1 with eculizumab treatment, patients showed a worsening in mean QMG score by Week 16 in Period 2 (during treatment with placebo). At the beginning of Period 2, those patients had a mean carryover effect of -6.5. By the end of Period 2, that mean change in QMG score had been reduced to -4.5.

Study observations indicate that discontinuation of eculizumab in a disease characterized by unremitting uncontrolled terminal complement activation exposes patients to the risk of substantial disease worsening as demonstrated by reappearance and/or deterioration of MG symptoms in clinically improved patients in Study ECU-MG-301, and worsened QMG score in Study C08-001 in patients who switched to placebo after treatment with eculizumab.

Post marketing experience

From post-marketing experience, the estimated exposure to Soliris since the first Marketing Authorisation in Mar 2007 to 01 Oct 2016 is 28,518 patient-years including 21,016 patient-years and 7,502 patient-years for PNH and aHUS respectively.

Alexion closely monitors the following risks for Soliris:

- Important identified risks: meningococcal infections, sepsis, serious infections, Aspergillus infection, severe TMA complications after discontinuation of eculizumab in aHUS patients, infusion reactions
- Important potential risks: serious haemolysis after discontinuation of eculizumab in PNH patients, malignancies and haematological abnormalities in PNH patients, immunogenicity, serious infection in neonates after maternal exposure to eculizumab
- Potential risks not categorized as important: cardiac disorders, cases with fatal outcome, reactions consistent with angioedema, and pyelonephritis
- Missing information: experience in pregnancy and lactation, children, and patients with hepatic impairment.

Based on a cumulative postmarketing exposure of approximately 28,518 patient-years and considering the 82 cumulative postmarketing reports of meningococcal infection, the reporting rate is estimated to be 0.29 per 100 patient-years. The fatal meningococcal infection rate is 0.03 per 100 patient-years.

Overall, the postmarketing reporting rate of meningococcal infection has continued to be consistent at approximately 0.5 or less per 100 patient-years.

Cumulative analysis of all serious infection data does not reveal any new safety concern. The risks of serious infections and sepsis (bacterial, viral, and fungal), particularly with encapsulated bacteria such as Neisseria species, are addressed in the EU RMP, in educational material for physicians and patients, and in product information (SmPC or United States Package Insert).

Combined (studies 301 and 302) safety analysis results

An interim analysis of Study ECU-MG-302 was performed with a clinical database cut-off date of 21 Sep 2016, in which all patients had been treated with eculizumab for at least 26 weeks (n = 108) with the exception of those who discontinued prior to Week 26.

Study duration and treatment duration in Study ECU-MG-302 from the 21 Sep 2016 clinical database cut-off are provided in Table 48 below. The median (range) duration of treatment with eculizumab for the placebo/eculizumab and eculizumab/eculizumab arms is 40.1 weeks (12.1 to 96.0 weeks) and 40.6 weeks (1 day to 92.1 weeks), respectively. Patients in the eculizumab/eculizumab arm had received an additional 26 weeks of treatment with eculizumab in Study ECU-MG-301, prior to enrolling in Study ECU-MG-302. In Studies ECU-MG-301 and ECU-MG-302 combined, 113 (91.9%) patients had been exposed to eculizumab for >6 months and 72 (58.5%) patients had been exposed to eculizumab for >12 months.

Table 48 Study Duration and Treatment Duration by Treatment Arm in Study ECU-MG-302 – Extension Safety Set

Variable	Statistic	Placebo/Eculizumab (N = 61)	Eculizumab/Eculizumab (N = 56)	Total (N = 117)
Study Duration (days)[a]	n	61	56	117
	Mean (SD)	349.7 (160.64)	339.3 (155.10)	344.7 (157.42)
	Median	294.0	292.5	294.0
	Min, Max	111, 694	78, 667	78, 694
	Total	21333	18999	40332
Duration of Treatment (days)[b]	n	61	56	117
	Mean (SD)	336.8 (159.65)	325.8 (159.55)	331.5 (159.01)
	Median	281.0	284.5	281.0
	Min, Max	85, 672	1, 645	1, 672
	Total	20546	18242	38788

a Study Duration = Date of Completion/Discontinuation (or death) - Date of Informed Consent + 1.
b Duration of Treatment = Last IP Dose Date - First IP Dose Date + 1.
Abbreviations: IP = investigational product; Max = maximum; Min = minimum

Safety analyses were also performed using the combined data from Study ECU-MG-301 (final analysis) and Study ECU-MG-302 (21 Sep 2016 clinical database cut-off). The incidence of TEAEs was assessed for all patients treated with eculizumab in Studies ECU-MG-301 and ECU-MG-302 to determine whether the frequency of AEs changes with increased exposure to eculizumab. The number of TEAEs, TESAEs, and AESIs are shown for the Combined Safety Set in Studies ECU-MG-301 and ECU-MG-302 by length of treatment in Table 2 for Months 0 to 15 and in Table 3 for Months 15 to 30.

Table 49 Summary of Treatment-Emergent Adverse Events by Exposure to Eculizumab from 0 to 15 Months – All Eculizumab-Treated Patients in Studies ECU-MG-301 and ECU-MG-302

Adverse Event Category System Organ Class	All Eculizumab Patients (N = 123)									
	0-3 Months (N = 123)		> 3 to 6 Months (N = 119)		> 6 to 9 Months (N = 113)		> 9 to 12 Months (N = 86)		> 12 to 15 Months (N = 72)	
	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
Any TEAE	362	94 (76.4)	274	76 (63.9)	216	77 (68.1)	166	50 (58.1)	121	45 (62.5)
Infections and Infestations	68	51 (41.5)	58	42 (35.3)	41	29 (25.7)	42	25 (29.1)	27	18 (25.0)
Any TESAE	18	12 (9.8)	16	12 (10.1)	18	15 (13.3)	13	8 (9.3)	14	7 (9.7)
Infections and Infestations	5	4 (3.3)	2	2 (1.7)	5	5 (4.4)	3	2 (2.3)	2	2 (2.8)
Any AESI	27	10 (8.1)	6	5 (4.2)	14	11 (9.7)	12	7 (8.1)	7	7 (9.7)

Notes: TEAEs are AEs with onset on or after the date of the first eculizumab dose for the patient. If a patient had more than one TEAE for a particular SOC, he/she is counted only once for that SOC. If a patient had more than one TEAE for a particular preferred term, he/she is counted only once for that preferred term. Patient percentages are based on the number of eculizumab patients in the Combined Safety Set for Studies ECU-MG-301 and ECU-MG-302 in each time period.
Abbreviations: AE = adverse event; AESI = adverse event of special interest; SOC = system organ class; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

Table 50 Summary of Treatment-Emergent Adverse Events by Exposure to Eculizumab from > 15 to 30 Months – All Eculizumab-Treated Patients in Studies ECU-MG-301 and ECU-MG-302

Adverse Event Category System Organ Class	All Eculizumab Patients (N = 123)									
	> 15 to 18 Months (N = 48)		> 18 to 21 Months (N = 28)		> 21 to 24 Months (N = 16)		> 24 to 27 Months (N = 9)		> 27 to 30 Months (N = 3)	
	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
Any TEAE	83	28 (58.3)	47	17 (60.7)	14	10 (62.5)	7	3 (33.3)	2	1 (33.3)
Infections and Infestations	15	9 (18.8)	7	5 (17.9)	4	3 (18.8)	2	2 (22.2)	0	0 (0.0)
Any TESAE	5	3 (6.3)	1	1 (3.6)	1	1 (6.3)	0	0 (0.0)	0	0 (0.0)
Infections and Infestations	1	1 (2.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Any AESI	6	4 (8.3)	7	6 (21.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

Notes: TEAEs are AEs with onset on or after the date of the first eculizumab dose for the patient. If a patient had more than one TEAE for a particular SOC, he/she is counted only once for that SOC. If a patient had more than one TEAE for a particular preferred term, he/she is counted only once for that preferred term. Patient percentages are based on the number of eculizumab patients in the Combined Safety Set for Studies ECU-MG-301 and ECU-MG-302 in each time period.
Abbreviations: AE = adverse event; AESI = adverse event of special interest; SOC = system organ class; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

The proportion of patients who experienced TEAEs was consistent over time with increased exposure to eculizumab (94 [76.4%] patients experiencing one or more TEAEs during Months 0 to 3 of treatment, 45 [62.5%] patients experiencing one or more TEAEs during Months 12 to 15), and 10 [62.5%] patients experiencing one or more TEAEs during Months 21 to 24). Similarly, the proportion of patients experiencing one or more TESAEs during the first 15 months of exposure to eculizumab did not increase over time.

The incidence of TEAEs in the SOC of Infections and infestations did not increase with increased exposure to eculizumab, with 51 (41.5%), 42 (35.3%), 29 (25.7%), 25 (29.1%), 18 (25.0%), 9 (18.8%), 5 (17.9%), 3 (18.8%), 2 (22.2%), and 0 (0.0%) of patients experiencing these events at Months 0 to 3, Months > 3 to 6, Months > 6 to 9, Months > 9 to 12, Months > 12 to 15, Months > 15 to 18, Months > 18 to 21, Months > 21 to 24, Months >24 to 27, and Months > 27 to 30, respectively. The incidence of TESAEs in the SOC of Infections and infestations did not increase with increased exposure to eculizumab, with rates of serious Infections and infestations of 4 (3.3%), 2 (1.7%), 5 (4.4%), 2 (2.3%), 2 (2.8%), 1 (2.1%), and 0 (0.0%) at Months 0 to 3, Months > 3 to 6, Months > 6 to 9, Months > 9 to 12, Months > 12 to 15, Months > 15 to 18, and Months > 18, respectively.

The proportion of patients experiencing AESIs, defined in Study ECU-MG-302 Clinical Study Report, remained consistent with increased exposure to eculizumab. Alexion pooled safety data across the Phase 2 and 3 refractory gMG clinical studies and calculated incidence rates of AESIs as a frequency per 100 patient-years, thereby enabling a comparison between placebo- and eculizumab-treated patients. While the eculizumab dose used in Phase 2 (600/900 mg) was lower than that in the Phase 3 studies (900/1200 mg), the overall contribution of Phase 2 to the combined dataset is small. Furthermore, the eculizumab safety database does not suggest any difference in safety profile across both dose regimens.

Table 51 provides incidence rates (frequency/100 patient-years) of AESIs comparing placebo and eculizumab in Studies C08-001, ECU-MG-301, and ECU-MG-302. Exposure in the eculizumab group is significantly greater (N = 136; PY = 139.9) compared to placebo (N = 76; PY = 34.8). Overall event rate (frequency/100 patient-years) of all AESIs is comparable across the 2 groups (placebo 51.7 versus eculizumab 56.5). For the SOC of Infections and infestations, the event rate was 20.1 for placebo versus 13.6 for eculizumab. Similarly, for infusion reactions (including selected Preferred Terms from the SOCs of General disorders, Immune system disorders, and Injury, poising and procedural complications), the event rate was 31.6 for placebo versus 33.6 for eculizumab. No AESIs of serious cutaneous reactions or angioedema were reported. For AESIs in the SOC of Cardiac disorders, the event rate was 0.0 for placebo compared to 9.3 for eculizumab. Adverse events of special interest noted in the SOC of Cardiac disorders include acute myocardial infarction (1), atrial fibrillation (6), tachycardia (5), and myocardial infarction (1). All of these events occurred after Month 6 of eculizumab exposure with the majority occurring after Month 9 of exposure (see Table 49). All patients with events of myocardial infarction and atrial fibrillation had

underlying cardiac disease prior to enrollment in the study, except for 1 patient who had transient atrial fibrillation in extremis.

The AESI of cardiac disorders was added as a potential risk not categorized as important, based on a PRAC request dated 10 Mar 2017 (signal of ventricular fibrillation should be monitored together with potential risk of cardiac disorders). The most recent Periodic Benefit-Risk Evaluation Report (PBRER) 14.1 submitted on 13 Jan 2017 that includes an analysis of cumulative data from all sources through 01 Oct 2016 has not revealed any new safety concerns, and proposed that the signal of cardiac disorders has been refuted and closed. Additionally, a more comprehensive examination of cardiac events seen across the eculizumab development program was submitted on 06 Apr 2017 as part of the PRAC request following its assessment of PBRER 14.1 (Procedure # PSUSA/00001198/201610).

Table 51 Treatment-Emergent Adverse Events of Special Interest by MedDRA SOC/Preferred Term and Treatment Group in MG Studies Based on Incidence Rates per 100 Patient-Years of Exposure

System Organ Class	Placebo (Studies C08-001 and ECU-MG-301) (N = 76; PY = 34.8)	Eculizumab (Studies C08-001, ECU-MG-301, and ECU-MG-302) (N = 136; PY = 139.9)
	Number of Events (ER)	Number of Events (ER)
All TEAEs of Special Interest	18 (51.7)	79 (56.5)
Cardiac disorders	0 (0.0)	13 (9.3)
Acute myocardial infarction	0 (0.0)	1 (0.7)
Atrial fibrillation	0 (0.0)	6 (4.3)
Myocardial infarction	0 (0.0)	1 (0.7)
Tachycardia	0 (0.0)	5 (3.6)
General disorders and administration site conditions	5 (14.4)	14 (10.0)
Generalised oedema	0 (0.0)	1 (0.7)
Infusion site pain	0 (0.0)	1 (0.7)
Infusion site pruritus	2 (5.7)	0 (0.0)
Injection site erythema	3 (8.6)	0 (0.0)
Oedema	0 (0.0)	1 (0.7)
Oedema peripheral	0 (0.0)	8 (5.7)
Peripheral swelling	0 (0.0)	3 (2.1)
Immune system disorders	3 (8.6)	1 (0.7)
Hypersensitivity	3 (8.6)	1 (0.7)
Infections and infestations	7 (20.1)	19 (13.6)
Bacteraemia	0 (0.0)	1 (0.7)
Bronchitis	0 (0.0)	1 (0.7)
Cytomegalovirus infection	0 (0.0)	1 (0.7)
Diverticulitis	0 (0.0)	2 (1.4)
Endocarditis	0 (0.0)	1 (0.7)
Gastroenteritis	2 (5.7)	1 (0.7)
Influenza	0 (0.0)	2 (1.4)
Pneumonia	0 (0.0)	2 (1.4)
Pseudomonal sepsis	0 (0.0)	1 (0.7)
Respiratory syncytial virus infection	0 (0.0)	1 (0.7)
Sepsis	0 (0.0)	3 (2.1)
Tonsillitis	1 (2.9)	1 (0.7)
Upper respiratory tract infection	2 (5.7)	1 (0.7)
Urinary tract infection	0 (0.0)	1 (0.7)
Urinary tract infection bacterial	1 (2.9)	0 (0.0)
Varicella	1 (2.9)	0 (0.0)
Injury, poisoning and procedural complications	3 (8.6)	32 (22.9)
Infusion related reaction	3 (8.6)	32 (22.9)

Abbreviations: ER = event rate; MedDRA = Medical Dictionary for Regulatory Activities; MG = myasthenia gravis; PY = patient years; SOC = System Organ Class; TEAEs = treatment-emergent adverse events

Table 52 and Table 53 address the issue of increasing toxicity with the long-term use of eculizumab. This table details the incidence of AESIs by 3-month treatment periods of the Combined Safety Set in Studies ECU-MG-301 and ECU-MG-302. There are no obvious trends or increases in any of the selected

events, other than cardiac disorders, which have been described above, observed after 6 months of exposure to eculizumab. The incidence of infections was maintained at approximately 2% to 3% up to 18 months of eculizumab exposure, and was 0% beyond Month 18; however, the number of patients exposed to eculizumab beyond 18 months was low (N = 28). Based on all available data, including over 10 years of experience in the 2 other indications for which eculizumab is approved, it is Alexion's assessment that the risk for any AESI does not increase with increased duration of treatment in refractory gMG patients.

Table 52 Treatment-Emergent Adverse Events of Special Interest by MedDRA SOC and Preferred Term by 3-Month Treatment Periods from 0 to 15 Months – Combined Safety Set of Studies ECU-MG-301 and ECU-MG-302

Adverse Event Category System Organ Class	All Eculizumab Patients (N = 123)									
	0 to 3 Months (N = 123)		> 3 to 6 Months (N = 119)		> 6 to 9 Months (N = 113)		> 9 to 12 Months (N = 86)		> 12 to 15 Months (N = 72)	
	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
All TEAEs of Special Interest	27	10 (8.1)	6	5 (4.2)	14	11 (9.7)	12	7 (8.1)	7	7 (9.7)
Cardiac disorders	0	0 (0.0)	0	0 (0.0)	1	1 (0.9)	5	4 (4.7)	4	4 (5.6)
Acute myocardial infarction	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (1.4)
Atrial fibrillation	0	0 (0.0)	0	0 (0.0)	1	1 (0.9)	1	1 (1.2)	2	2 (2.8)
Myocardial infarction	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (1.2)	0	0 (0.0)
Tachycardia	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	3	3 (3.5)	1	1 (1.4)
General disorders and administration site conditions	3	3 (2.4)	1	1 (0.8)	5	5 (4.4)	2	1 (1.2)	1	1 (1.4)
Generalised oedema	0	0 (0.0)	1	1 (0.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Infusion site pain	1	1 (0.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Oedema	0	0 (0.0)	0	0 (0.0)	1	1 (0.9)	0	0 (0.0)	0	0 (0.0)
Oedema peripheral	1	1 (0.8)	0	0 (0.0)	3	3 (2.7)	2	1 (1.2)	1	1 (1.4)
Peripheral swelling	1	1 (0.8)	0	0 (0.0)	1	1 (0.9)	0	0 (0.0)	0	0 (0.0)
Immune system disorders	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Hypersensitivity	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Infections and infestations	5	4 (3.3)	3	3 (2.5)	5	5 (4.4)	3	2 (2.3)	2	2 (2.8)
Bacteraemia	1	1 (0.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Bronchitis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (1.4)
Cytomegalovirus infection	0	0 (0.0)	0	0 (0.0)	1	1 (0.9)	0	0 (0.0)	0	0 (0.0)
Diverticulitis	1	1 (0.8)	1	1 (0.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Endocarditis	1	1 (0.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Gastroenteritis	1	1 (0.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Influenza	0	0 (0.0)	0	0 (0.0)	2	2 (1.8)	0	0 (0.0)	0	0 (0.0)
Pneumonia	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (1.2)	0	0 (0.0)
Pseudomonal sepsis	0	0 (0.0)	0	0 (0.0)	1	1 (0.9)	0	0 (0.0)	0	0 (0.0)
Respiratory syncytial virus infection	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (1.2)	0	0 (0.0)
Sepsis	0	0 (0.0)	1	1 (0.8)	0	0 (0.0)	1	1 (1.2)	1	1 (1.4)
Tonsillitis	0	0 (0.0)	0	0 (0.0)	1	1 (0.9)	0	0 (0.0)	0	0 (0.0)
Upper respiratory tract infection	1	1 (0.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Urinary tract infection	0	0 (0.0)	1	1 (0.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Injury, poisoning and procedural complications	19	4 (3.3)	2	1 (0.8)	3	2 (1.8)	2	1 (1.2)	0	0 (0.0)
Infusion related reaction	19	4 (3.3)	2	1 (0.8)	3	2 (1.8)	2	1 (1.2)	0	0 (0.0)

Notes: TEAEs of Special Interest are AEs of Special Interest with an onset on or after the date of the first Eculizumab dose in the patient. If a patient had more than one TEAE for a particular SOC, he/she is counted only once for that SOC. If a patient had more than one TEAE for a particular Preferred Term, he/she is counted only once for that Preferred Term. Patient percentages are based on the number of Eculizumab patients in the ECU-MG-301 and ECU-MG-302 Combined Safety Set in each time period.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; TEAE = treatment-emergent adverse event

Table 53 Treatment-Emergent Adverse Events of Special Interest by MedDRA SOC and Preferred Term by 3-Month Treatment Periods from 15 to 30 Months – Combined Safety Set of Studies ECU-MG-301 and ECU-MG-302

Adverse Event Category System Organ Class	All Eculizumab Patients (N = 123)									
	> 15 to 18 Months (N = 48)		> 18 to 21 Months (N = 28)		> 21 to 24 Months (N = 16)		> 24 to 27 Months (N = 9)		> 27 to 30 Months (N = 3)	
	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)
All TEAEs of Special Interest	6	4 (8.3)	7	6 (21.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Cardiac disorders	1	1 (2.1)	2	2 (7.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Acute myocardial infarction	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Atrial fibrillation	0	0 (0.0)	2	2 (7.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Myocardial infarction	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Tachycardia	1	1 (2.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
General disorders and administration site conditions	1	1 (2.1)	1	1 (3.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Generalised oedema	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Infusion site pain	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Oedema	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Oedema peripheral	0	0 (0.0)	1	1 (3.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Peripheral swelling	1	1 (2.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Immune system disorders	0	0 (0.0)	1	1 (3.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Hypersensitivity	0	0 (0.0)	1	1 (3.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Infections and infestations	1	1 (2.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Bacteraemia	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Bronchitis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Cytomegalovirus infection	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Diverticulitis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Endocarditis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Gastroenteritis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Influenza	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Pneumonia	1	1 (2.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Pseudomonal sepsis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Respiratory syncytial virus infection	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Sepsis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Tonsillitis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Upper respiratory tract infection	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Urinary tract infection	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Injury, poisoning and procedural complications	3	2 (4.2)	3	2 (7.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Infusion related reaction	3	2 (4.2)	3	2 (7.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

Notes: TEAEs of Special Interest are AEs of Special Interest with an onset on or after the date of the first Eculizumab dose in the patient. If a patient had more than one TEAE for a particular SOC, he/she is counted only once for that SOC. If a patient had more than one TEAE for a particular Preferred Term, he/she is counted only once for that Preferred Term. Patient percentages are based on the number of Eculizumab patients in the ECU-MG-301 and ECU-MG-302 Combined Safety Set in each time period.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; TEAE = treatment-emergent adverse event

The patient who died during Study ECU-MG-302 experienced no TEAEs during Months 0 through 6 of treatment. However, between Months 6 and 9 of treatment, the patient experienced 6 TESAEs (DIC, CMV infection, pyrexia, histiocytosis haematophagic, sepsis, and hepatic failure) and died. More information is provided in the safety narrative for the Patient.

Based on these data, no trends were observed with increased exposure to eculizumab; however, the number of patients was smaller at later time points (> 24 months, N = 9; and > 27 months, N = 3).

Comparing the frequency of TEAEs by age, there does not appear to be any trend toward increased incidence of events in the older age group with the exception of squamous cell carcinoma and falls, both of which could be related directly to older age. TEAEs that occurred in > 1 patient > 65 years of age are shown by Preferred Term, age, and treatment arm in Table 54.

Table 54 Treatment-Emergent Adverse Events by Preferred Term, Age, and Treatment Arm Occurring in > 1 Patient > 65 Years of Age in Study ECU-MG-302 – Safety Set

Preferred term	Age 18 to 65 years (N = 97)				Age > 65 years (N = 20)			
	Placebo/Eculizumab (N = 50)		Eculizumab/Eculizumab (N = 47)		Placebo/Eculizumab (N = 11)		Eculizumab/Eculizumab (N = 9)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Patients with TEAEs	362	44 (88.0)	384	43 (91.5)	114	11 (100.0)	65	9 (100.0)
Arthralgia	3	3 (6.0)	12	9 (19.1)	1	1 (9.1)	2	1 (11.1)
Back pain	7	6 (12.0)	2	1 (2.1)	1	1 (9.1)	1	1 (11.1)
Bronchitis	3	3 (6.0)	9	5 (10.6)	1	1 (9.1)	1	1 (11.1)
Cellulitis	1	1 (2.0)	0	0 (0.0)	1	1 (9.1)	1	1 (11.1)
Contusion	0	0 (0.0)	5	3 (6.4)	4	2 (18.2)	3	1 (11.1)
Cystitis	0	0 (0.0)	0	0 (0.0)	3	2 (18.2)	0	0 (0.0)
Dry Eye	1	1 (2.0)	1	1 (2.1)	1	1 (9.1)	1	1 (11.1)
Dyspepsia	1	1 (2.0)	2	2 (4.3)	3	2 (18.2)	1	1 (11.1)
Fall	1	1 (2.0)	2	2 (4.3)	2	2 (18.2)	6	3 (33.3)
Fatigue	3	2 (4.0)	3	3 (6.4)	2	2 (18.2)	1	1 (11.1)
Gastroenteritis viral	1	1 (2.0)	2	2 (4.3)	3	2 (18.2)	1	1 (11.1)
Headache	24	16 (32.0)	13	10 (21.3)	7	4 (36.4)	1	1 (11.1)
Influenza	3	3 (6.0)	5	5 (10.6)	1	1 (9.1)	2	1 (11.1)
Influenza like illness	1	1 (2.0)	2	2 (4.3)	2	1 (9.1)	1	1 (11.1)
Infusion related reaction	23	4 (8.0)	5	3 (6.4)	3	2 (18.2)	0	0 (0.0)
Insomnia	1	1 (2.0)	3	3 (6.4)	1	1 (9.1)	1	1 (11.1)
Muscle spasms	3	3 (6.0)	1	1 (2.1)	1	1 (9.1)	1	1 (11.1)
Myalgia	13	6 (12.0)	4	3 (6.4)	1	1 (9.1)	1	1 (11.1)
Myasthenia gravis	9	7 (14.0)	12	8 (17.0)	1	1 (9.1)	1	1 (11.1)
Nasopharyngitis	13	10 (20.0)	16	13 (27.7)	4	3 (27.3)	2	2 (22.2)
Nausea	6	5 (10.0)	5	4 (8.5)	3	3 (27.3)	0	0 (0.0)
Neck pain	2	2 (4.0)	3	3 (6.4)	1	1 (9.1)	1	1 (11.1)
Rash	4	2 (4.0)	0	0 (0.0)	1	1 (9.1)	2	1 (11.1)
Squamous cell carcinoma	1	1 (2.0)	0	0 (0.0)	6	3 (27.3)	1	1 (11.1)
Urticaria	0	0 (0.0)	0	0 (0.0)	1	1 (9.1)	1	1 (11.1)

Notes: TEAEs are AEs with a start date on or after the first dose date in the study. If a patient had more than one TEAE for a particular preferred term, he/she is counted only once for that preferred term. Patient percentages are based on the total number of patients in the Safety Set in the particular treatment arm or overall.
Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event
Source: Study ECU-MG-302 CSR

Overall, the safety profile of eculizumab in refractory gMG patients appears consistent with the known safety profile in indications for which eculizumab is already approved (PNH and aHUS). The incidence of serious infections in this population is comparable to that observed in other populations in which eculizumab has been studied. There have been no cases of meningococcal infection in this study as of the 21 Sep 2016 database cut-off. The safety profile observed in patients in the eculizumab/eculizumab arm during Study ECU-MG-302 was similar to that observed in eculizumab-treated patients in Study ECU-MG-301, and no new safety signals were observed in this extension study.

2.5.1. Discussion on clinical safety

The eculizumab clinical development programme for refractory gMG consisted of 3 clinical studies, the completed Phase 3 Study ECU-MG-301, its extension Study ECU-MG-302 still ongoing and the supportive Phase 2 Study C08-001.Overall, 133 patients were exposed to eculizumab as of the cut-off date of March 2016 (47.1 patient years of exposure). Of them, a total of 62 patients were treated with the proposed dosing regimen during the initial 26 weeks of the pivotal study and 58/62 entered into the extension phase and continued on eculizumab. Additional 55 out of the 63 patients that were initially assigned to placebo arm entered the extension study and received eculizumab. This is considered the main safety database in support of the claimed indication, bearing in mind that the extension study (Study ECU-MG-302) is currently ongoing and only 72 (58.5%) patients had been exposed to eculizumab for > 12 months.

The extent of the safety database is limited, in particular long-term safety data. This is a drawback for such a chronic indication. However, given the low prevalence of gMG, drug exposure can be considered acceptable for the short-term safety assessment of eculizumab but long-term data remain limited.

An interim analysis of Study ECU-MG-302 was performed with a clinical database cut-off date of 21 Sep 2016, in which all patients had been treated with eculizumab for at least 26 weeks (n = 108) with the

exception of those who discontinued prior to Week 26. Safety analyses were also performed using the combined data from Study ECU-MG-301 (final analysis) and Study ECU-MG-302 (21 Sep 2016 clinical database cut-off). A total of 113 (91.9%) patients had been exposed to eculizumab for > 6 months and 72 (58.5%) patients had been exposed to eculizumab for > 12 months.

Nevertheless, it is noted that the knowledge gained on the safety of eculizumab in the already authorised indications provides some support to the limited safety database in gMG, particularly in aHUS given that the proposed posology is the same.

Overall, treatment groups were well-balanced with respect to demographic and disease baseline characteristics. The majority of patients were white (approximately 75%) and more than 65% women. The mean age was 47 years (ranging from 19 to 80 years). Half of the patients had a MGFA disease classification of III (moderate weakness affecting other than ocular weakness) in both treatment arms and 13.3% class IV in eculizumab treatment arm (8% in placebo). Half of the patients had been treated with at least 3 ISTs. Overall, the studied population can be considered representative of the intended target indication, although given the limited number of patients some subgroups are underrepresented.

Overall, 14 patients discontinued in Studies ECU-MG-301 and ECU-MG-302, the majority while being treated with eculizumab. Patient's decision was the first cause of treatment discontinuation (7/14; 5 on eculizumab, 2 on placebo) followed by AEs (5/14 patients, all on eculizumab).

In general treatment with eculizumab was well tolerated. The overall incidence of AEs was similar between study arms (85.5% eculizumab versus 89% placebo), most of them mild-moderate AEs (severe AEs 25.4% placebo versus 12.9% eculizumab) and 48.4% in eculizumab versus 39.7% in placebo considered related to treatment. SAEs were reported by 14.5% of patients in eculizumab treatment arm versus 28.6% in placebo. The incidence of AEs leading to treatment discontinuation is also low (6.5% eculizumab versus 0 placebo). 2 fatal cases were reported in the eculizumab treatment arm, in which the contribution of eculizumab to the outcome cannot be totally ruled out.

From the data presented, it seems that the underlying condition is contributing to a high extent to the overall reporting of AEs in both treatment arms. It also appears that eculizumab might mitigate the severity and seriousness of these events, based on the lower incidence of severe and SAEs in the eculizumab treated arm.

Headache (16.1% versus 19.0% of patients for eculizumab and placebo, respectively), upper respiratory infection (16.1% versus 19.0%), nasopharyngitis (14.5% versus 15.9%), nausea (12.9% versus 14.3%), diarrhoea (12.9% versus 12.7%), myasthenia gravis (9.7% versus 17.5%) were the most frequently reported AEs both in eculizumab and placebo groups. During the open-label extension nasopharyngitis (17.7%), headache (16.8%), diarrhoea (10.6%) and MG (8.8%) were also the most frequently reported AEs. Except for headache (reported by 22.4% of patients on placebo/eculizumab and 10.9% of patients on eculizumab/eculizumab) no relevant differences were observed if patients were previously treated with eculizumab or not. The most commonly reported severe AEs were myalgia, pyrexia and myasthenia gravis in eculizumab treatment group during the initial placebo-controlled period.

A total of 27 patients reported serious AEs in Study ECU-MG-301, 9 (14.5%) in patients treated with eculizumab and 18 (28.6%) in those on placebo. Eighteen patients (15.9%) reported SAEs in Study ECU-MG-302. Apart from SAEs related to the condition, the most frequently reported SAEs were those related to infections (both in placebo and eculizumab groups), and gastrointestinal disorders.

Adverse events of special interest included infections (meningococcal infections, aspergillus infections, and any serious infection), sepsis, infusion-related reactions, serious cutaneous reactions, cardiac disorders, and angioedema. During the controlled study more patients on placebo (11 versus 4) reported an AESI. Nevertheless, for the individual AESIs a higher incidence of infections in the eculizumab treatment arm versus placebo is noted, which appears to increase with continued treatment. This should be taken cautiously because due to the limited number of patients minor numerical changes may substantially modify

the relative estimations. The MAH has presented an updated summary of the overall incidence of AESI by exposure (patient-years). No relevant differences with respect to placebo have been shown except for infusion related reactions (event rate versus placebo 8.6; eculizumab 22.9) and cardiac disorders (event rate placebo 0.0; eculizumab 9.3). The cardiac events are being followed and analysed by the PRAC. Although no clear safety signal appears to be identified, the long-term cardiovascular safety is being further characterized in this population. Currently ongoing Study MG-ECU-302 will provide further data. No meningococcal infections have been reported.

Due to the limited number of patients enrolled in some categories, it is not possible to obtain any reliable conclusions about different safety profile in specific subgroups. Nevertheless, a trend for a higher incidence of AEs and SAEs is noted in the elderly population. As requested, the MAH has provided further clarification. The number and percentage of subjects ≥ 65 years of age (n = 23) is rather small. It can be agreed that no alarming signals related to age (even with more prolonged exposure) were detected during the studies, but the limited number of subjects enrolled precludes from making a sound conclusion. Adequate wording to reflect the limited number of elderly subjects has been included in the SmPC. Further information on long-exposure to eculizumab in this subgroup is expected from the ongoing extension Study ECU-MG-302. Lastly, given the long-half-life of eculizumab, rebound phenomenon would not be expected. The limited information provided is reassuring in this regard.

The safety data from the Phase 2 study are consistent with the findings from the Phase 3 studies, and do not highlight any specific concerns.

From the updated information provided it should be noted that the exposure to eculizumab beyond 12 months is still limited. In Studies ECU-MG-301 and ECU-MG-302 combined, 113 (91.9%) patients had been exposed to eculizumab for > 6 months and 72 (58.5%) patients had been exposed to eculizumab for > 12 months. No relevant safety concerns have been raised with respect to the previous assessment and also to other indications.

The long-term safety profile of eculizumab in myasthenia gravis patients is still incomplete. The main limitations are related to the low number of patients and the exposure to the medicinal product.

2.5.2. Conclusions on clinical safety

In general treatment with eculizumab was well tolerated and the safety profile is considered acceptable for the intended adult target population. From the data presented, it seems that the underlying condition is contributing to a high extent to the overall reporting of AEs in both treatment arms. Eculizumab does not appear to substantially increase toxicity - in fact the incidence of severe and SAEs was lower in the eculizumab treatment arm than in placebo. However, these conclusions should be taken with caution given the limited safety database.

Overall, the AE profile is consistent with that known for eculizumab in other indications, with no unexpected findings. With the caution needed due to the limitations of the long-term safety database, it appears that the overall toxicity does not increase with continued treatment. However, in order to make a more informed assessment of the safety of eculizumab in the treatment of patients with refractory gMG, particularly the long-term safety, an update of the safety database based on the extension Study ECU-MG-302 should be presented annually.

2.5.3. Periodic Safety Update Report cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted RMP:

The PRAC considered that the risk management plan version 16.2 is acceptable.

The CHMP endorsed this advice without changes.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

Safety concerns

Table 55 Summary of the safety concerns

Important Identified risks	• Meningococcal infections • Sepsis • Serious infections • *Aspergillus* infection • Severe TMA complications due to drug discontinuation in aHUS patients • Infusion reactions
Important potential risk	• Serious haemolysis after drug discontinuation in PNH patients • Malignancies and haematologic abnormalities in PNH patients • Immunogenicity • Serious infections in neonates after maternal exposure to eculizumab
Missing information	• Use in pregnant and lactating women • Long term safety in aHUS patients

Abbreviations: aHUS = atypical haemolytic uremic syndrome; PNH = paroxysmal nocturnal haemoglobinuria; TMA = thrombotic microangiopathy

Pharmacovigilance plan

Table 56 On-going and planned additional pharmacovigilance studies / activities in the Pharmacovigilance Plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
M07-001 "PNH REGISTRY" (Non-interventional, 3*)	To collect and evaluate safety data specific to the use of SOLIRIS and to collect data to characterize the progression of PNH as well as clinical outcomes, mortality and morbidity in SOLIRIS and non-SOLIRIS treated patients.	- Meningococcal infections - Sepsis - Serious infections, including *Aspergillus* infection - Infusion reactions -Serious haemolysis after drug discontinuation in PNH patients - Malignancies and hematologic abnormalities in PNH patients - Immunogenicity - Use in pregnant and lactating women - Use in patients with hepatic impairment	Ongoing	Yearly interim data analysis report.
M11-001 "aHUS REGISTRY" (Non-interventional, 3*)	To collect and evaluate safety and effectiveness data specific to the use of eculizumab in aHUS patients To assess the long-term manifestations of TMA complications of aHUS as well as other clinical outcomes, including mortality and morbidity in aHUS patients receiving eculizumab treatment or other disease management.	- Meningococcal infections - Sepsis - Serious infections, including *Aspergillus* infection - Severe TMA complications due to drug discontinuation in aHUS patients - Infusion reactions - Immunogenicity - Use in pregnant and lactating women - Use in patients with hepatic impairment - Long term safety in aHUS patients	Ongoing	Yearly interim data analysis report
C11-003 "An observational, multi-center, multi-national long term follow-up study of atypical haemolytic uremic syndrome (aHUS) patients treated with eculizumab in a prior clinical study" (Non-interventional, 3*)	To assess the long-term efficacy and safety of eculizumab in patients with aHUS who have previously participated in an eculizumab clinical study.	Long term safety in aHUS patients	Ended Final study report under preparation	Final study report will be submitted along with PSUR#15 in December 2017

Abbreviations: aHUS = atypical haemolytic uremic syndrome; PNH = paroxysmal nocturnal haemoglobinuria; TMA = thrombotic microangiopathy

Risk minimisation measures

Table 57 Summary of the risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Meningococcal infection	**See text in the SmPC sections 4.3, 4.4 and 4.8**	**Educational Material** - Physician's Guide to Prescribing -Patient tool kit - The Patient Safety Card - The PNH, aHUS or refractory gMG Patient/Parent information brochure - The PNH, aHUS or refractory gMG Parent information brochure **Controlled distribution** **Vaccination reminders to HCP**
Sepsis	**See text in the SmPC sections 4.4 and 4.8**	**Educational Material** -The Physician's Guide to Prescribing -Patient tool kit - The Patient Safety Card - The PNH, aHUS or refractory gMG Patient/Parent information brochure - The PNH or aHUS Parent information brochure
Serious infection	**See text in the SmPC sections 4.4 and 4.8**	**Educational Material** -The Physician's Guide to Prescribing -Patient tool kit - The Patient Safety Card - The PNH, aHUS or refractory gMG Patient/Parent information brochure - The PNH or aHUS Parent information brochure
Aspergillus infection	**See text in the SmPC sections 4.4 and 4.8**	**Educational material** -The Physician's Guide to Prescribing
Severe TMA complications due to discontinuation in aHUS patients	**See text in the SmPC section 4.4**	**Educational Material** -The Physician's Guide to Prescribing - The aHUS Patient/Parent information brochure - The aHUS Parent information brochure
Infusion reactions	**See text in the SmPC sections 4.2, 4.4 and 4.8**	**Educational Material** - The Physician's Guide to Prescribing - The PNH, aHUS or refractory gMG Patient/Parent information brochure - The PNH or aHUS Parent information brochure
Serious haemolysis after drug discontinuation in PNH	**See text in the SmPC section 4.4**	**Educational Material** -The Physician's Guide to Prescribing - The PNH Patient/Parent information brochure - The PNH Parent information brochure
Malignancies and haematologic abnormalities in PNH	**See text in the SmPC section 4.8**	None proposed
Immunogenicity	**See text in the SmPC sections 4.4**	**Educational Material**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and 4.8	- The Physician's Guide to Prescribing
Serious infections in neonates after maternal exposure to eculizumab	**See text in the SmPC section 4.6 and in Package Leaflet section 2**	None proposed
Use in pregnant and lactating women	**See text in the SmPC section 4.6**	**Educational Material** - The Physician's Guide to Prescribing - The PNH, aHUS or refractory gMG Patient/Parent information brochure - The PNH or aHUS Parent information brochure
Long-term safety in aHUS and refractory gMG patients	**See text in the SmPC section 5.1**	None proposed

Abbreviations: aHUS = atypical haemolytic uremic syndrome; gMG = generalised myasthenia gravis; HCP = healthcare professional; PNH = paroxysmal nocturnal haemoglobinuria; SmPC = Summary of Product Characteristics TMA = thrombotic microangiopathy

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

The main changes related to the procedure are listed below (deletions are marked with ~~striketrough~~ and additions with underlined text):

4.1 Therapeutic indication

Soliris is indicated in adults and children for the treatment of ~~patients with~~:
- Paroxysmal nocturnal haemoglobinuria (PNH).
  Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1).
- Atypical haemolytic uremic syndrome (aHUS) (see section 5.1).

Soliris is indicated in adults for the treatment of
- Refractory generalized myasthenia gravis (gMG) in patients who are anti-acetylcholine receptor (AChR) antibody-positive (see section 5.1).

4.2 Posology and method of administration

Soliris must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological ~~and/or~~, renal or neuromuscular disorders.
……..
In atypical Haemolytic Uremic Syndrome (aHUS) and refractory generalized Myasthenia Gravis (gMG):
The aHUS and refractory gMG dosing regimen for adult patients (≥18 years of age) consists of a 4 week initial phase followed by a maintenance phase:
……..

Soliris has not been studied in paediatric patients with refractory gMG.

……..

Refractory gMG
Available data suggest that clinical response is usually achieved by 12 weeks of Soliris treatment. Continued therapy should be carefully reconsidered in a patient who shows no evidence of therapeutic benefit by 12 weeks.

4.4 Special warnings and precautions for use

……..

Immunogenicity

…….

In a refractory gMG placebo controlled study, none (0/62) of the Soliris treated patients showed antidrug antibody response during the 26 week active treatment.

…….

Immunosuppressant and anticholinesterase therapies
Patients in refractory gMG clinical trials continued treatment with immunosuppressant and anticholinesterase therapies while on Soliris treatment. Withdrawal of immunosuppressant and anticholinesterase therapies during Soliris treatment for refractory gMG was not assessed in the placebo-controlled studies. In the open-label extension trial (Study ECU-MG-302), physicians had the option to adjust background immunosuppressant therapies. In this setting, a decrease of the daily dose of at least 1 immunosuppressant was observed in 47% of patients. The most common reason for change in immunosuppressant therapy was improvement in MG symptoms while on eculizumab treatment. When immunosuppressant and anticholinesterase therapies are decreased or discontinued, patients should be monitored closely for signs of disease exacerbation.

……..

Treatment discontinuation for refractory gMG:
Use of Soliris in refractory gMG treatment has been only studied in the setting of chronic administration. Patients that discontinue Soliris treatment should be carefully monitored for signs and symptoms of deterioration of disease.

Apart from the changes listed above, related changes to sections 4.8 and 5.1 of the SmPC were also introduced and can be found in the published product information.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for Soliris is for the treatment of refractory gMG patients in adult patients who are AChR Ab-positive.

Myasthenia gravis is an autoimmune disease in which Abs bind to AChRs or to functionally related molecules in the postsynaptic membrane at the NMJ. The Abs induce a fluctuating pronounced weakness of skeletal muscles. Muscular exertion increases the myasthenic weakness, initially focal weakness of extrinsic ocular muscles. In the majority of patients, the symptoms progress and proceed to affect other bulbar muscles as well as limb muscles (gMG).

3.1.2. Available therapies and unmet medical need

There are two basic approaches to management of MG: targeting the physiological effects (increasing the amount of AChR in synaptic cleft) or targeting the underlying autoimmune mechanism of the disease, using short-term immune therapies such as plasmapheresis or IVIg, and long-term immune therapies with immunosuppressive agents such as corticosteroids and immunosuppressive drugs). Thymectomy is also a treatment option. A group of patients, however, have a very difficult to- control disease despite of being treated with available therapy. These patients are often referred to as having treatment-refractory myasthenia. Myasthenia gravis is a rare disease, considered to affect less than 2 in 10,000 people in the European Union. The intended population represents a subset accounting for approximately 10% of patients with generalised disease.

3.1.3. Main clinical studies

The clinical programme for eculizumab in the treatment of refractory gMG patients consisted of one Phase III clinical trial (study ECU-MG-301), one open-label extension study currently ongoing (Study ECU-MG-302), and one exploratory phase II study
(Study C08-001).

The pivotal studies recruited patients ≥18 years with confirmed diagnosis of MG (determined by the presence of AChR Abs and electrophysiological/ pharmacological confirmation) with suboptimal response to multiple immunosuppressive agents.

Study ECU-MG-301 was a randomized, double-blind, parallel-group, placebo-controlled, multicenter trial to evaluate the safety and efficacy of eculizumab for the treatment of patients with refractory gMG. A dosing regimen of 900 mg weekly for 4 weeks followed by 1200 mg for the 5th dose and then every two weeks was administered. Rescue therapy was indicated in case of worsening (MG crisis, significant worsening of any of the MG-ADL items except ocular one or physician's judgment) and subjects who were rescued remained in the trial. After completing the 26-week Study Period, patients were provided the opportunity to enter an extension study (Study ECU-MG-302) to receive open-label eculizumab. A total of 125 gMG patients were randomized to placebo (n = 63) and eculizumab (n = 62).

Eculizumab or placebo was added on top of patient background therapy and no changes were allowed during the study. The evaluation of efficacy was based primarily on the assessment of the clinical status of the patient, based on MG symptoms (MG-ADL) and signs (QMG). Several related definitions of responders were used as secondary endpoints. Other specific scales (MGC) and the impact of the change in the quality of life (MG-QoL15) were also assessed.

Study ECU-MG-302 is an ongoing Phase 3, open-label, long-term extension study. Patients who completed Study ECU-MG-301 were eligible for entry into this extension study. The duration of the clinical trial is 4 years and it is currently ongoing.

Study C08-001was a randomized, double-blind, placebo-controlled, cross-over, multicenter study to evaluate the safety and efficacy of eculizumab for the treatment of patients with refractory gMG. Patients were treated with the eculizumab dosage regimen approved for PNH (600/900 mg) during two 16-week treatment periods with a 5-week wash out period between them. A total of 14 patients were treated in Period 1 (7 eculizumab/7 placebo) and 12 patients were treated in Period 2 (6 eculizumab/6 placebo).

3.2. Favourable effects

The proposed dosing regimen for the treatment of refractory gMG is 900 mg weekly for 4 weeks followed by 1200 mg for the 5th dose and then every two weeks. This dose is identical to that approved for the treatment

of aHUS. Pharmacokinetic/PD model and Pop-PK/PD analysis performed with data from Studies ECU-MG-301 and C08-001 showed that at the selected dose 87% of the patients achieved the concentration required for complete complement inhibition(<20% cRBC haemolysis), with 92% achieving free C5 concentration of <0.5 µg /mL. The figures for 600/900 doses were 75% and 77%, respectively.

According to the pivotal trial results, after 26 weeks, more patients treated with eculizumab (900/1200 mg) than those treated with placebo achieved a positive response from the patient's (MG-ADL) and the physician's perspective (QMG). In MG-ADL a decrease of 4.7 points was observed in the eculizumab arm versus 2.8 points in the placebo group. In QMG Score a statistically significant difference was shown between treatment groups (-5.4 versus -2.4; p=0.0129), with a difference recognised as a clinically significant treatment effect. When the effect was assessed in terms of responders, a significantly higher response was observed in both scales (MG-ADL responders difference 20%, p=0.029; QMG responders difference 26.2%, p=0.0018) in patients treated with eculizumab.

Statistically significant differences were also observed in the main Quality of Life measure (Worst-Rank ANCOVA p=0.0281) where the improvement observed was -6.5 points in placebo compared to -13.5 points in eculizumab group.

Long-term efficacy data are provided by Study ECU-MG-302, still ongoing. Results from the interim analysis indicate a positive effect on the maintenance of the response to eculizumab. When patients who received placebo in the Study ECU-MG-301 were treated with eculizumab in Study ECU-MG-302 an improvement similar to that showed by patients on active treatment in the previous study was observed. In patients previously treated with eculizumab the response was consistently maintained through Study ECU-MG-302. At Week 26 of Study ECU-MG-302 responder rates were similar between both treatment arms (MG-ADL: eculizumab/eculizumab 65.3% versus placebo/eculizumab 69.1%; QMG: eculizumab/eculizumab 43.8% versus placebo/eculizumab 47.3%).

Eculizumab (or placebo) was added on top of patient background therapy and no changes were allowed during the Study MG-ECU-301. In Study MG-ECU-302, the majority of patients were receiving concomitant treatment at entry. During this extension study the concomitant treatment could be adapted. There were more patients who had dose reduction or stopped immunosuppressive medication than those who had dose increases or started new immunosuppresants.

3.3. Uncertainties and limitations about favourable effects

The primary analysis (Worst-Rank ANCOVA) shows that the treatment with eculizumab during 26 weeks failed to meet the primary endpoint (mean change in MG-ADL score from baseline to Week 26). This was attributed to the handling of discontinuations in the method of analysis reflected in the final SAP version. Analysis of covariance for primary and secondary end-point was performed on ranks and not on raw score changes, adding to the difficulty to have a clear view of the clinical impact of the drug on patients. The analysis finally conducted, ranking on death and MG crisis in addition to use of rescue, dropout and endpoint score is not obviously aligned to the stated primary endpoint aiming to estimate the treatment effect on change from baseline to week 26 of the endpoint score (eg, MG-ADL).

Some additional analyses of the main variable (MG-ADL) and the key secondary endpoint (physician-assessed QMGe) were provided. The tipping point ANCOVA sensitivity analyses as well as ANCOVA and Repeated Measures sensitivity analyses predefined in the final SAP showed a consistent separation between eculizumab and placebo effect. Statistically significant differences were also shown when Repeated Measures analysis was conducted imputing missing data using the response seen on placebo.

Concerns related to the clinical relevance of the observed effect were raised. The effect size of all conducted analyses (both the primary and the sensitivity analyses) was smaller than the 2-point reduction a priori defined as clinically relevant in the patient reported scale. The MCID was justified at individual level (absolute change from baseline in individual patients) rather than as a measure of difference between groups. Although this approach was partially agreed in the sense of isolating the eculizumab effect, it cannot be deemed as an absolute proof of clinically meaningful results given the absence of comparison versus placebo and as a consequence the lack of discussion in terms of relative efficacy. Of note, a difference of 2.5 in mean changes from baseline for MG-ADL (mean change from baseline of 4 for eculizumab and 1.5 for placebo) was assumed in the sample size estimation.

The main secondary endpoint QMG scores could provide an alternative insight of the effect size, since a more clear separation between groups was observed in all the analyses conducted. However, this outcome is not time-weighted as scores at intermediate time points are ignored and this is of interest in a fluctuating condition. This time aspects are partially informed by patient-reported MG-ADL score, given that it provides information over the prior 7 days. In relation to this issue, the responder rates reported through the study show a regular effect during the 26 week-study period both from the patient's (MG-ADL) and physician's perspective, suggesting the clinical relevance of the effect in a time-weighted manner. Importantly, these exploratory analyses of responders appear to point out a clinically meaningful result along the 26 weeks of the study.

It seems to be related to greater than predicted response in the placebo group, which is surprising given that the population recruited was a heavily treated (and still symptomatic) group of patients with little room for improvement according to the procedures of the trial (no dose adjustment of concomitant treatment was allowed). It is also confirmed when the effect was expressed in terms of responder rate, where 40% of placebo patients (versus 60% of eculizumab patients) fulfilled the response definition. This was explained to likely be due to patients and physician expectations, the trial procedures and the fluctuating nature of the condition, even though the latter was not clearly observable in the results as there seemed to be a plateau in the curve of placebo group. A number of clinical trials in MG are reported in literature in which similar placebo effect was shown. Whereas differences in intervention, number of patients, severity of the condition and concomitant treatment do not allow easy comparisons to Study ECU-MG-301, they offer some support to the placebo effect reported in Study MG-ECU-301, which was considered reassuring.

Myasthenia Gravis QoL results are congruent with the clinical endpoints but one relevant issue would be what the observed change represents for the patients and to what extent it is reflecting a clinically relevant improvement because of treatment. Statistically significant differences were shown in the QoL questionnaire (MG-QoL 15). Both placebo and eculizumab groups showed a score reduction (QoL improvement) with respect to baseline. While the magnitude of change is beyond the clinical meaningfulness (as defined in literature) for eculizumab, this is not the case for placebo. Indeed, some uncertainties still remain (eg, the minimal importance clinical difference with respect to placebo), but overall, bearing in mind that QoL results provide additional positive dimensions to the objective clinical measurements, the global efficacy data are considered reassuring.

Supplementary information from PD parameters do not provide further support in elucidating the effect or identifying a population where the benefit is more pronounced. No correlation could be established between AChR antibodies levels during the study and the response to treatment. Also, no relationship was observed between eculizumab exposure and MG-ADL, QMG, MGC, or clinical deterioration. Examination by subgroups was not informative, mainly due to the limited number of patients in some subgroups.

There are uncertainties related to the maintenance of the effect over time due to the low number of patients and follow-up period. Preliminary assessment suggests a positive effect on the maintenance of the response to eculizumab. When patients on placebo in the Study ECU-MG-301 were treated with eculizumab in Study ECU-MG-302 an improvement similar to that showed by patients on active treatment in the previous

study was observed. In patients previously treated with eculizumab the response was consistently maintained through Study ECU-MG-302. However, longer term data (efficacy and safety) are warranted, given the chronic condition of gMG and the need of treatment with eculizumab in these patients.

3.4. Unfavourable effects

The overall incidence of AEs was similar between study arms (85.5% eculizumab versus 89% placebo), most of them mild-moderate AEs (severe AEs 25.4% placebo versus 12.9% eculizumab) and 48.4% in eculizumab versus 39.7% in placebo considered related to treatment. Serious AEs were reported by 14.5% of patients in eculizumab treatment arm versus 28.6% in placebo. The incidence of AEs leading to treatment discontinuation is also low (6.5% eculizumab versus 0 placebo). Two (2) fatal cases were reported in the eculizumab treatment arm, in which the contribution of eculizumab to the outcome cannot be totally ruled out.

Headache (16.1% versus 19.0% of patients for eculizumab and placebo, respectively), upper respiratory infection (16.1% versus 19.0%), nasopharyngitis (14.5% versus 15.9%), nausea (12.9% versus 14.3%), diarrhea (12.9% versus 12.7%), myasthenia gravis (9.7% versus 17.5%) were the most frequently reported AEs both in eculizumab and placebo groups. During the open-label extension nasopharyngitis (17.7%), headache (16.8%), diarrhoea (10.6%) and myasthenia gravis (8.8%) were also the most frequently reported AEs. Except for headache (reported by 22.4% of patients on placebo/eculizumab and 10.9% of patients on eculizumab/eculizumab) no relevant differences were observed if patients were previously treated with eculizumab or not. The most commonly reported severe AEs were myalgia, pyrexia and myasthenia gravis in eculizumab treatment group during the initial placebo-controlled period.

A total of 27 patients reported serious AEs in Study ECU-MG-301, 9 (14.5%) in patients treated with eculizumab and 18 (28.6%) in those on placebo. Apart from SAEs related to the condition, the most frequently reported SAEs were those related to infections (both in placebo and eculizumab groups), and gastrointestinal disorders.

3.5. Uncertainties and limitations about unfavourable effects

The main uncertainties of the unfavourable effects derive from the limitations of the safety database, particularly long-term safety data. These uncertainties are mitigated to some extent by the current experience with eculizumab use in other chronic conditions.

Due to the limited number of patients enrolled in some categories, it is not possible to obtain any reliable conclusions about different safety profile in specific subgroups. Nevertheless, a trend for a higher incidence of AEs and SAEs is noted in the elderly population.

Lastly, given the long-half-life of eculizumab, rebound phenomenon is not expected and the limited information provided is reassuring in this regard. However, information of disease outcomes following treatment discontinuation is very scarce.

3.6. Effects Table

Table 58 Effects Table for Soliris in the treatment of Myasthenia Gravis in adults

Effect	Short Description	Unit	Eculizumab	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
MG-ADL	Change from baseline. Ranked score LS mean Absolute mean change from baseline		56.6 -4.7	68.3 -2.8	Difference -11.7; Non-significant. Sensitivity analysis (ANCOVA, repeated-measured method) showed statistically significant differences, though magnitude of the effects remain modest	Study ECU-MG-301
	Proportion of responders (with >3 points of improvement)	%	59.7	39.7	Difference (95%CI) 20.0 (2.8, 37.2) p=0.0229	
QMG	Ranked score LS mean Absolute mean change from baseline		54.7 -5.4	70.7 -2.4	Differences in LS Means -16 (-28.5, -3.43), p 0.0129 Sensitivity analysis show consistent results (ANCOVA, repeated-measured method)	
	Proportion of responders		45.2	19	Difference (95%CI) 26.2 (10.4, 41.8) p=0.0018	
MG Composite Total Score	LS Mean		-7.8	-5.0	Difference -2.8 (-5.43, -0.12), p 0.0406	
MG QoL 15 total score	Ranked score LS Mean		55.5	69.7	Difference -14.3, p 0.0281	
Unfavourable Effects						
AEs		%	94.3	88.9	Percentages calculated on the basis of available data from 123 patients on eculizumab and 63 patients on PBO.	ECU-MG-301/ ECU-MG-302 Combined safety analysis
Treatment-Related AEs			55.3	39.7		
Severe AE			27.6	25.4		
SAE			33.3	28.6		
AE leading to treatment discontinuation			4.9	0		
Headache			31.7	19.0		ECU-MG-301/ ECU-MG-302 Combined safety analysis
URTI			14.6	19.0		
Nasopharyngitis			26.0	15.9		
Nausea			15.4	14.3		
Diarrhoea			17.1	12.7		
MG			16.3	17.5		

Notes: MG-ADL, change: 8 items, not weighted, individually graded from 0 (normal) to 3 (most severe), providing a total MG-ADL score ranging from 0 to 24. QMG: 13 items, each graded from 0 (normal) to 3 (most severe), providing a total QMG score ranging from 0 to 39 points. MGC, possible cumulative scores range from 0 to 50, with higher scores representing greater morbidity. MG-QoL15, consisting of 15 questions with responses to each questioned scored from 0 (not at all) to 4 (quite a bit), and possible cumulative scores ranging from 0 to 60

Abbreviations: AE = adverse event; ANCOVA = Analysis of Covariance; CI = confidence interval; LS = least squares; MCID = minimal clinically important difference; MG = myasthenia gravis; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGC = Myasthenia Gravis Composite score; MG-QoL15 = Myasthenia Gravis Quality of Life 15-item Scale; PBO = placebo; QMG = Quantitative Myasthenia Gravis for Disease Severity; SAE = serious adverse event; URTI = upper respiratory tract infection

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Although statistically significant differences over placebo have not been formally demonstrated for the primary endpoint, based on mean change in MG-ADL score from baseline to week 26 (Worst-Rank ANCOVA), sensitivity analyses conducted and relevant secondary endpoints, including physician assessment of improvement (QMG total score), responder analysis for MG-ADL and QMG total score, and QoL questionnaires, reached statistical significant differences in favour of eculizumab. The clinical relevance of these differences, i.e. the actual benefit for patients, is difficult to elucidate, particularly since the magnitude of the differences are on the verge of those differences considered clinically relevant by available medical literature in the field. Additionally, it is recognised that the intended target population are adult MG patients refractory to available treatment options, where a limited improvement would be expected and for which an unmet medical need is fully agreed. With the caution needed due to the limitations of the safety database, particularly in the long-term, it is considered that the safety profile of eculizumab in patients with gMG is consistent with that already known, which is reassuring. In general treatment with eculizumab was well tolerated, with a low incidence of SAE, severe AEs and AE leading to treatment discontinuation. Two deaths were reported, in which the potential contribution of eculizumab could not be ruled out.

3.7.2. Balance of benefits and risks

A consistent effect appears to be measured in the disease-specific scales tested. The fact of lack of statistical significant in the primary endpoint, seems to be related to the method applied when it comes to managing the missing data. Exploratory analyses with alternative methods, in some way less conservative than Worst Rank analysis would support this hypothesis. In addition, the secondary variables and the responder analyses seem to suggest a clinical meaningful result.

Of note, the total number of patients requiring rescue therapy (19% versus 10%; placebo versus eculizumab respectively) and the total number of patients reporting clinical deterioration (24% versus 10%; placebo versus eculizumab respectively) are also reassuring.

The presented results from Study ECU-MG-302 give support to the eculizumab effect seen during the placebo-controlled phase. The improvement observed in the specific scales was maintained during the reported period. The fact that patients in placebo improved when they were treated with eculizumab in Study ECU-MG-302 is also supportive along with the steroid-sparing effect of eculizumab, with a greater proportion of patients who had dose reductions or stopped ≥ 1 IST (47%) than those who had dose increases or started ≥1 IST (16.2%), would add further evidence of the eculizumab effect.

The remaining uncertainties on the primary efficacy analysis (MICD versus placebo) mean that it would be difficult to conclude that the treatment would be applicable to a broader MG population, but in the case of the difficult-to control population in a debilitating condition (as the population recruited in the Phase 3 clinical trials) this is clearly justified. In this sense, the proposed indication “Refractory gMG in patients who are AChR Ab-positive (see section 5.1)” was considered acceptable.

It appears that the maximal improvement is achieved in the first 12 weeks of treatment and little benefit is added beyond this time point. A close patient monitoring would allow to early identify responders to eculizumab so that it could be discontinued if the response is not reached.

In general, treatment with eculizumab was well tolerated and the safety profile is considered acceptable for the intended target population. From the data presented, it seems that the underlying condition is contributing to a high extent to the overall reporting of AEs in both treatment arms. Eculizumab appears not

to substantially increase toxicity, in fact the incidence of severe and SAEs was lower in the eculizumab treatment arm than in placebo. However, these conclusions should be taken with caution given the limited safety database.

In addition, the overall AE profile is consistent with that known for eculizumab in other chronic conditions, with no unexpected findings, which is reassuring and mitigates the limitations of the safety database in MG. However, the long-term efficacy of eculizumab in this population need to be further documented. The experience on long term exposure to eculizumab and the detection of AEs which could occur within a long latency is still limited. Therefore long-term safety data from ongoing Study MG-ECU-302 should be submitted in order to further inform on the lasting effects and safety of the product.

In short, there seem to be a proven effect of eculizumab in the treatment of refractory gMG in adult patients who are AChR Ab-positive. While clinical relevance of that effect could be considered insufficiently characterised, it has been shown that the addition of eculizumab on top of background therapy offers a better result in decreasing the number and severity of symptoms of refractory MG. Bearing in mind this fact along with the absence of an incremental toxicity, the benefits exceed the risks associated with this treatment.

3.8. Conclusions

The overall Benefit/Risk balance of Soliris in the treatment of refractory gMG in adult patients who are anti-AChR Ab-positive is positive.

The CHMP considers the following measures necessary to address the outstanding issues related to pharmacology, long-term efficacy and safety:

- *Long-term stability (LTS) programs are currently ongoing to cover storage of samples from Study ECU-MG-301. Stability data for eculizumab PK (assay IM-1727-112), free C5, and haemolytic long-term storage samples will be available following the final analysis in Q3-Q4 2017. The Applicant should submit the stability data when available*
- *The applicant should submit annual updates of the open-label extension Study ECU-MG-302. Final study results should be provided when available to confirm long term efficacy and safety.*

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication of Soliris to include the treatment of refractory generalised myasthenia gravis in adult patients who are AChR antibody-positive; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated to include information on the new indication and to include the new methodology to

calculate the Adverse Drug Reaction frequencies (section 4.8). The Package Leaflet and RMP (finally agreed version 15.2) are updated accordingly.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the RMP.

This recommendation is subject to the following amended condition:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Additional risk minimisation measures

The MAH shall agree the details of a controlled drug distribution system and educational material including a patient safety card with each National Competent Authority and must implement such programmes nationally to ensure that:

1. All healthcare practitioners who may prescribe eculizumab receive the appropriate educational material;

2. All patients being treated with eculizumab receive a patient safety card;

3. Drug distribution will only be possible after written confirmation that the patient received or will receive meningococcal vaccination and/or antibiotic prophylaxis;

4. Vaccination reminders are sent to the prescribers.

The educational material should be agreed with the National Competent Authority and should contain the following:

- SmPC;
- Physician's guides to prescribing;
- Patient's/carer's information brochures;
- Patient safety card.

The **physician's guides** to prescribing should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection and sepsis, especially of *Neisseria meningitides;*
- All patients must be monitored for signs of meningitis;
- The need for patients to be vaccinated against *Neisseria meningitidis* two weeks prior to receiving eculizumab and/or to receive antibiotic prophylaxis;
- The requirement to vaccinate children against pneumococcus and *Haemophilus influenzae* before eculizumab treatment;
- There is an important risk of Aspergillus infection in patients treated with eculizumab. The healthcare professionals should be advised to look for risk factors and signs and symptoms of Aspergillus infection. Practical advice should be included to mitigate the risk;
- The risk of infusion reactions including anaphylaxis and advice on post-infusion monitoring;
- No clinical data on exposed pregnancies is available. Eculizumab should be given to a pregnant woman only if clearly needed. The need for effective contraception in women of childbearing potential during and up to five months after treatment. Breast-feeding should be discontinued during and up to five months after treatment;
- The risk of developing antibodies to eculizumab;

- The safety concerns in children;

- Risk of serious haemolysis following eculizumab discontinuation and postponement of administration, its criteria, the required post-treatment monitoring and its proposed management (PNH only);

- Risk of severe thrombotic microangiopathic complications following eculizumab discontinuation and postponement of administration, its signs, symptoms, monitoring and management (aHUS only);

- Risk of substantial disease exacerbation or relapse following eculizumab discontinuation (refractory gMG only);

- The need to explain to and ensure understanding of by patients/carers:
  - the risks of treatment with eculizumab;
  - the signs and symptoms of sepsis/severe infection and what action to take;
  - the patient's/carer's guides and their contents;
  - the need to carry the patient safety card and to tell any healthcare practitioner that he/she is receiving treatment with eculizumab;
  - the requirement for vaccinations/antibiotic prophylaxis;
  - the enrolment in the registries;

- Details of the PNH and aHUS registries and how to enter patients.

The **patient's/carer's guides** should be indication specific and contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection, especially *Neisseria meningitides;*

- Signs and symptoms of severe infection and the need to obtain urgent medical care;

- The patient safety card and the need to carry it on their person and tell any treating healthcare professional that they are being treated with eculizumab;

- The importance of meningococcal vaccination prior to treatment with eculizumab and/or to receive antibiotic prophylaxis;

- The need for children to be vaccinated against pneumococcus and *Haemophilus influenzae* before eculizumab treatment;

- The risk of infusion reactions with eculizumab, including anaphylaxis, and the need for clinical monitoring post-infusion;

- That eculizumab may be teratogenic and the need for effective contraception in women of childbearing potential during and up to five months after treatment, and that breast-feeding should be discontinued during and up to five months after treatment;

- Risk of severe TMA complications (in aHUS) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations;

- Risk of serious haemolysis (in PNH) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations;

- Risk of substantial disease exacerbation or relapse (in refractory gMG) following discontinuation/postponement of eculizumab administrations and recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations;

- Enrolment in the PNH and aHUS registries;

- The safety concerns in children.

The **patient safety card** should contain:

- Signs and symptoms of infection and sepsis;
- Warning to seek immediate medical care if above are present;
- Statement that the patient is receiving eculizumab;
- Contact details where a HCP can receive further information.

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense eculizumab, a reminder in order that prescriber/pharmacist checks if a (re)-vaccination against Neisseria meningitidis is needed for his/her patients on eculizumab.

5. European Public Assessment Report changes

The European Public Assessment Report (EPAR) will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication of Soliris to include the treatment of refractory generalised myasthenia gravis in adult patients who are AChR antibody-positive; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated to include information on the new indication and to include the new methodology to calculate the ADR frequencies (section 4.8). The Package Leaflet and RMP (finally agreed version 15.2) are updated accordingly.

Summary

Please refer to the scientific discussion Soliris-H-C-791-II-0090 for further information.

Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 22 June 2017.