CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125166Orig1s422

Trade Name:	Soliris
Generic or Proper Name:	Eculizumab concentrated solution for intravenous infusion, 300 mg (10 mg/mL)
Sponsor:	Alexion Pharmaceuticals, Inc.
Approval Date:	October 23, 2017
Indication:	For the use of Soliris (eculizumab) for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetycholine receptor (AchR) antibody positive and for proposed modifications for the proposed REMS.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166Orig1s422

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125166/S-422

SUPPLEMENT APPROVAL

Alexion Pharmaceuticals, Inc.
Attention: Mr. Michael Page
Senior Director, Regulatory Affairs
100 College Street
New Haven, CT 06510

Dear Mr. Page:

Please refer to your Supplemental Biologics License Application (sBLA), dated December 23, 2016, received December 23, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Soliris® (eculizumab) concentrated solution for intravenous infusion, 300 mg (10 mg/mL).

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated December 23, 2016.

This Prior Approval supplemental biologics application provides for the use of Soliris® (eculizumab) for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive and for proposed modifications to the approved REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the prescribing information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Soliris® (eculizumab) was originally approved on June 4, 2010, and the most recent modification was approved on January 13, 2017. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of editorial changes to the REMS document and changes to the REMS appended materials to align with labeling changes related to the new indication.

Your proposed modified REMS, submitted on October 23, 2017, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on April 30, 2014.

There are no changes to the REMS assessment plan described in our September 15, 2015, letter.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125166 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 125166 REMS ASSESSMENT

NEW SUPPLEMENT BLA 125166/ S-XXX
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125166/ S-XXX
PRIOR APPROVAL SUPPLEMENT PROPOSED
MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125166/ S-XXX
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT S-XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR/BLA 125166/ S-XXX
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR BLA 125166

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Michelle Mathers, Regulatory Project Manager, at michelle.mathers@fda.hhs.gov or at (240) 402-2645.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
10/23/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SOLIRIS safely and effectively. See full prescribing information for SOLIRIS.

SOLIRIS® (eculizumab) injection, for intravenous use
Initial U.S. Approval: 2007

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. (See *Warnings and Precautions* (5.1) for additional guidance on the management of the risk of meningococcal infection.)**
- **Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program (5.2).

RECENT MAJOR CHANGES

Indications and Usage (1.3)	10/2017
Dosage and Administration (2.3, 2.4)	10/2017

INDICATIONS AND USAGE

Soliris is a complement inhibitor indicated for:

- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis (1.1).
- The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (1.2).

  Limitation of Use
  Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- The treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive (1.3).

DOSAGE AND ADMINISTRATION

For intravenous infusion only
PNH Dosage Regimen: (2.1)
aHUS Dosage Regimen: (2.2)
gMG Dosage Regimen (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/30 mL (10 mg/mL) in single-dose vial (3).

CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection (4).
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection (5.1).

WARNINGS AND PRECAUTIONS

- Discontinue Soliris in patients who are being treated for serious meningococcal infections (5.4).
- Use caution when administering Soliris to patients with any other systemic infection (5.2).

ADVERSE REACTIONS

The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea (6.1).

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥20%) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections, pyrexia (6.1).

The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial (≥10%) is: musculoskeletal pain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, Soliris may cause fetal harm (8.1).

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2017

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early [*see Warnings and Precautions (5.1)*].

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection. [See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of meningococcal infection].**
- **Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program [*see Warnings and Precautions (5.2)*]. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

1 INDICATIONS AND USAGE

1.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

Soliris is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.

1.2 Atypical Hemolytic Uremic Syndrome (aHUS)

Soliris is indicated for the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

Limitation of Use

Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

1.3 Generalized Myasthenia Gravis (gMG)

Soliris is indicated for the treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe Soliris must enroll in the Soliris REMS [*see Warnings and Precautions (5.2)*].

Vaccinate patients according to current ACIP guidelines to reduce the risk of serious infection [*see Warnings and Precautions (5.1) and (5.2)*].

Only administer as an intravenous infusion.

2.1 Recommended Dosage Regimen – PNH

For patients 18 years of age and older, Soliris therapy consists of:

- 600 mg weekly for the first 4 weeks, followed by
- 900 mg for the fifth dose 1 week later, then
- 900 mg every 2 weeks thereafter.

Administer Soliris at the recommended dosage regimen time points, or within two days of these time points *[see Warnings and Precautions (5.4)*].

2.2 Recommended Dosage Regimen – aHUS

For patients 18 years of age and older, Soliris therapy consists of:

- 900 mg weekly for the first 4 weeks, followed by
- 1200 mg for the fifth dose 1 week later, then
- 1200 mg every 2 weeks thereafter.

For patients less than 18 years of age, administer Soliris based upon body weight, according to the following schedule (Table 1):

Table 1: Dosing Recommendations in Patients Less Than 18 Years of Age

Patient Body Weight	Induction	Maintenance
40 kg and over	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks

30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

Administer Soliris at the recommended dosage regimen time points, or within two days of these time points.

2.3 Recommended Dosage Regimen – gMG

For patients with generalized Myasthenia Gravis, Soliris therapy consists of:

- 900 mg weekly for the first 4 weeks, followed by
- 1200 mg for the fifth dose 1 week later, then
- 1200 mg every 2 weeks thereafter.

Administer Soliris at the recommended dosage regimen time points, or within two days of these time points.

2.4 Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion

For adult and pediatric patients with aHUS and adult patients with gMG, supplemental dosing of Soliris is required in the setting of concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion (PE/PI) (Table 2).

Table 2: Supplemental Dose of Soliris after PE/PI

Type of Plasma Intervention	Most Recent Soliris Dose	Supplemental Soliris Dose With Each Plasma Intervention	Timing of Supplemental Soliris Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	≥600 mg	600 mg per each plasmapheresis or	

		plasma exchange session	
Fresh frozen plasma infusion	≥300 mg	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

2.5 Preparation

Dilute Soliris to a final admixture concentration of 5 mg/mL using the following steps:

- Withdraw the required amount of Soliris from the vial into a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Soliris to a final concentration of 5 mg/mL by adding the appropriate amount (equal volume of diluent to drug volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP to the infusion bag.

The final admixed Soliris 5 mg/mL infusion volume is 60 mL for 300 mg doses, 120 mL for 600 mg doses, 180 mL for 900 mg doses or 240 mL for 1200 mg doses (Table 3).

Table 3: Preparation and Reconstitution of Soliris

Soliris Dose	Diluent Volume	Final Volume
300 mg	30 mL	60 mL
600 mg	60 mL	120 mL
900 mg	90 mL	180 mL
1200 mg	120 mL	240 mL

Gently invert the infusion bag containing the diluted Soliris solution to ensure thorough mixing of the product and diluent. Discard any unused portion left in a vial, as the product contains no preservatives.

Prior to administration, the admixture should be allowed to adjust to room temperature [18°-25° C, 64-77° F]. The admixture must not be heated in a microwave or with any heat source other than ambient air temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.6 Administration

Do Not Administer As An Intravenous Push or Bolus Injection

Administer the Soliris admixture by intravenous infusion over 35 minutes in adults and 1 to 4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion

pump. Admixed solutions of Soliris are stable for 24 h at 2-8° C (36-46° F) and at room temperature.

If an adverse reaction occurs during the administration of Soliris, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time should not exceed two hours in adults. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.

3 DOSAGE FORMS AND STRENGTHS

Injection: 300 mg single-dose vials each containing 30 mL of 10 mg/mL sterile, colorless, preservative-free eculizumab solution.

4 CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Meningococcal Infections

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. The use of Soliris increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis).

Vaccinate for meningococcal disease according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations, considering the duration of Soliris therapy.

Immunize patients without a history of meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris. If urgent Soliris therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible.

In prospective clinical studies, 75/100 patients with aHUS were treated with Soliris less than 2 weeks after meningococcal vaccination and 64 of these 75 patients received antibiotics for prophylaxis of meningococcal infection until at least 2 weeks after meningococcal vaccination. The benefits and risks of antibiotic prophylaxis for

prevention of meningococcal infections in patients receiving Soliris have not been established.

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical studies, 2 out of 196 PNH patients developed serious meningococcal infections while receiving treatment with Soliris; both had been vaccinated [*see Adverse Reactions (6.1)*]. In clinical studies among non-PNH patients, meningococcal meningitis occurred in one unvaccinated patient. In addition, 3 out of 130 previously vaccinated patients with aHUS developed meningococcal infections while receiving treatment with Soliris [*see Adverse Reactions (6.1)*].

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if an infection is suspected. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Discontinue Soliris in patients who are undergoing treatment for serious meningococcal infections.

5.2 Soliris REMS

Because of the risk of meningococcal infections, Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program.

Prescribers must counsel patients about the risk of meningococcal infection, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccine(s).

Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

5.3 Other Infections

Soliris blocks terminal complement activation; therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. Additionally, Aspergillus infections have occurred in immunocompromised and neutropenic patients. Children treated with Soliris may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib) infections according to ACIP guidelines. Use caution when administering Soliris to patients with any systemic infection [*see Warnings and Precautions (5.1)*].

5.4 Monitoring Disease Manifestations after Soliris Discontinuation

Treatment Discontinuation for PNH

Monitor patients after discontinuing Soliris for at least 8 weeks to detect hemolysis.

Treatment Discontinuation for aHUS

After discontinuing Soliris, monitor patients with aHUS for signs and symptoms of thrombotic microangiopathy (TMA) complications for at least 12 weeks. In aHUS clinical trials, 18 patients (5 in the prospective studies) discontinued Soliris treatment. TMA complications occurred following a missed dose in 5 patients, and Soliris was reinitiated in 4 of these 5 patients.

Clinical signs and symptoms of TMA include changes in mental status, seizures, angina, dyspnea, or thrombosis. In addition, the following changes in laboratory parameters may identify a TMA complication: occurrence of two, or repeated measurement of any one of the following: a decrease in platelet count by 25% or more compared to baseline or the peak platelet count during Soliris treatment; an increase in serum creatinine by 25% or more compared to baseline or nadir during Soliris treatment; or, an increase in serum LDH by 25% or more over baseline or nadir during Soliris treatment.

If TMA complications occur after Soliris discontinuation, consider reinstitution of Soliris treatment, plasma therapy [plasmapheresis, plasma exchange, or fresh frozen plasma infusion (PE/PI)], or appropriate organ-specific supportive measures.

5.5 Thrombosis Prevention and Management

The effect of withdrawal of anticoagulant therapy during Soliris treatment has not been established. Therefore, treatment with Soliris should not alter anticoagulant management.

5.6 Infusion Reactions

Administration of Soliris may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion reaction which required discontinuation of Soliris. Interrupt Soliris infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Meningococcal Infections [*see Warnings and Precautions (5.1)*]
- Other Infections [*see Warnings and Precautions (5.3)*]
- Monitoring Disease Manifestations After Soliris Discontinuation [*see Warnings and Precautions (5.4)*]
- Thrombosis Prevention and Management [*see Warnings and Precautions (5.5)*]
- Infusion Reactions [*see Warnings and Precautions (5.6)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Meningococcal infections are the most important adverse reactions experienced by patients receiving Soliris. In PNH clinical studies, two patients experienced meningococcal sepsis. Both patients had previously received a meningococcal vaccine. In clinical studies among patients without PNH, meningococcal meningitis occurred in one unvaccinated patient. Meningococcal sepsis occurred in one previously vaccinated patient enrolled in the retrospective aHUS study during the post-study follow-up period [*see Warnings and Precautions (5.1)*].

PNH

The data described below reflect exposure to Soliris in 196 adult patients with PNH, age 18-85, of whom 55% were female. All had signs or symptoms of intravascular hemolysis. Soliris was studied in a placebo-controlled clinical study (PNH Study 1, in which 43 patients received Soliris and 44, placebo); a single arm clinical study (PNH Study 2); and a long term extension study (E05-001). 182 patients were exposed for greater than one year. All patients received the recommended Soliris dose regimen.

Table 4 summarizes the adverse reactions that occurred at a numerically higher rate in the Soliris group than the placebo group and at a rate of 5% or more among patients treated with Soliris.

Table 4: Adverse Reactions Reported in 5% or More of Soliris Treated Patients with PNH and Greater than Placebo in the Controlled Clinical Study

Reaction	Soliris N = 43 N (%)	Placebo N = 44 N (%)
Headache	19 (44)	12 (27)
Nasopharyngitis	10 (23)	8 (18)
Back pain	8 (19)	4 (9)
Nausea	7 (16)	5 (11)
Fatigue	5 (12)	1 (2)
Cough	5 (12)	4 (9)
Herpes simplex infections	3 (7)	0
Sinusitis	3 (7)	0
Respiratory tract infection	3 (7)	1 (2)
Constipation	3 (7)	2 (5)
Myalgia	3 (7)	1 (2)
Pain in extremity	3 (7)	1 (2)
Influenza-like illness	2 (5)	1 (2)

In the placebo-controlled clinical study, serious adverse reactions occurred among 4 (9%) patients receiving Soliris and 9 (21%) patients receiving placebo. The serious reactions included infections and progression of PNH. No deaths occurred in the study and no patients receiving Soliris experienced a thrombotic event; one thrombotic event occurred in a patient receiving placebo.

Among 193 patients with PNH treated with Soliris in the single arm, clinical study or the follow-up study, the adverse reactions were similar to those reported in the placebo-controlled clinical study. Serious adverse reactions occurred among 16% of the patients in these studies. The most common serious adverse reactions were: viral infection (2%), headache (2%), anemia (2%), and pyrexia (2%).

aHUS

The safety of Soliris therapy in patients with aHUS was evaluated in four prospective, single-arm studies, three in adult and adolescent patients (Studies C08-002A/B, C08-003A/B, and C10-004), one in pediatric and adolescent patients (Study C10-003), and one retrospective study (Study C09-001r).

The data described below were derived from 78 adult and adolescent patients with Studies C08-002A/B, C08-003A/B and C10-004All patients received the recommended dosage of Soliris. Median exposure was 67 weeks (range: 2-145 weeks). Table 5 summarizes all adverse events reported in at least 10% of patients in Studies C08-002A/B, C08-003A/B and C10-004 combined.

Table 5: Per Patient Incidence of Adverse Events in 10% or More Adult and Adolescent Patients Enrolled in Studies C08-002A/B, C08-003A/B and C10-004Separately and in Total

	Number (%) of Patients			
	C08-002A/B (n=17)	**C08-003A/B (n=20)**	**C10-004 (n=41)**	**Total (n=78)**
Vascular Disorders				
Hypertension[a]	10 (59)	9 (45)	7 (17)	26 (33)
Hypotension	2 (12)	4 (20)	7 (17)	13 (17)
Infections and Infestations				
Bronchitis	3 (18)	2 (10)	4 (10)	9 (12)
Nasopharyngitis	3 (18)	11 (55)	7 (17)	21 (27)
Gastroenteritis	3 (18)	4 (20)	2 (5)	9 (12)
Upper respiratory tract infection	5 (29)	8 (40)	2 (5)	15 (19)
Urinary tract infection	6 (35.3)	3 (15)	8 (20)	17 (22)
Gastrointestinal Disorders				
Diarrhea	8 (47)	8 (40)	12 (32)	29 (37)
Vomiting	8 (47)	9 (45)	6 (15)	23 (30)
Nausea	5 (29)	8 (40)	5 (12)	18 (23)
Abdominal pain	3 (18)	6 (30)	6 (15)	15 (19)
Nervous System Disorders				
Headache	7 (41)	10 (50)	15 (37)	32 (41)
Blood and Lymphatic System Disorders				
Anemia	6 (35)	7 (35)	7 (17)	20 (26)
Leukopenia	4 (24)	3 (15)	5 (12)	12 (15)
Psychiatric Disorders				

	Number (%) of Patients			
	C08-002A/B (n=17)	**C08-003A/B (n=20)**	**C10-004 (n=41)**	**Total (n=78)**
Insomnia	4 (24)	2 (10)	5 (12)	11 (14)
Renal and Urinary Disorders				
Renal Impairment	5 (29)	3 (15)	6 (15)	14 (18)
Proteinuria	2 (12)	1 (5)	5 (12)	8 (10)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	4 (24)	6 (30)	8 (20)	18 (23)
General Disorders and Administration Site Conditions				
Fatigue	3 (18)	4 (20)	3 (7)	10 (13)
Peripheral edema	5 (29)	4 (20)	9 (22)	18 (23)
Pyrexia	4 (24)	5 (25)	7 (17)	16 (21)
Asthenia	3 (18)	4 (20)	6 (15)	13 (17)
Eye Disorder	5 (29)	2 (10)	8 (20)	15 (19)
Metabolism and Nutrition Disorders				
Hypokalemia	3 (18)	2 (10)	4 (10)	9 (12)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (6)	6 (30)	1 (20)	8 (10)
Skin and Subcutaneous Tissue Disorders				
Rash	2 (12)	3 (15)	6 (15)	11 (14)
Pruritus	1 (6)	3 (15)	4 (10)	8 (10)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	1 (6)	2 (10)	7 (17)	10 (13)
Back pain	3 (18)	3 (15)	2 (5)	8 (10)

[a] includes the preferred terms hypertension, accelerated hypertension, and malignant hypertension.

In Studies C08-002A/B, C08-003A/B and C10-004 combined, 60% (47/78) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were infections (24%), hypertension (5%), chronic renal failure (5%), and renal impairment (5%). Five patients discontinued Soliris due to adverse events; three due to worsening

renal function, one due to new diagnosis of Systemic Lupus Erythematosus, and one due to meningococcal meningitis.

Study C10-003 included 22 pediatric and adolescent patients, of which 18 patients were less than 12 years of age. All patients received the recommended dosage of Soliris. Median exposure was 44 weeks (range: 1 dose-87 weeks).

Table 6 summarizes all adverse events reported in at least 10% of patients enrolled in Study C10-003.

Table 6: Per Patient Incidence of Adverse Reactions in 10% or More Patients Enrolled in StudyC10-003

	1 month to <12 yrs (n=18)	**Total (n=22)**
Eye Disorders	3 (17)	3 (14)
Gastrointestinal Disorders		
Abdominal pain	6 (33)	7 (32)
Diarrhea	5 (28)	7 (32)
Vomiting	4 (22)	6 (27)
Dyspepsia	0	3 (14)
General Disorders and Administration Site Conditions		
Pyrexia	9 (50)	11 (50)
Infections and Infestations		
Upper respiratory tract infection	5 (28)	7 (32)
Nasopharyngitis	3 (17)	6 (27)
Rhinitis	4 (22)	4 (18)
Urinary Tract infection	3 (17)	4 (18)
Catheter site infection	3 (17)	3 (14)
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	2 (11)	3 (14)
Nervous System Disorders		
Headache	3 (17)	4 (18)
Renal and Urinary Disorders	3 (17)	4 (18)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	7 (39)	8 (36)
Oropharyngeal pain	1 (6)	3 (14)

	1 month to <12 yrs (n=18)	Total (n=22)
Skin and Subcutaneous Tissue Disorders		
Rash	4 (22)	4 (18)
Vascular Disorders		
Hypertension	4 (22)	4 (18)

In Study C10-003, 59% (13/22) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were hypertension (9%), viral gastroenteritis (9%), pyrexia (9%), and upper respiratory infection (9%). One patient discontinued Soliris due to an adverse event (severe agitation).

Analysis of retrospectively collected adverse event data from pediatric and adult patients enrolled in Study C09-001r (N=30) revealed a safety profile that was similar to that which was observed in the two prospective studies. Study C09-001rincluded 19 pediatric patients less than 18 years of age. Overall, the safety of Soliris in pediatric patients with aHUS enrolled in Study C09-001r appeared similar to that observed in adult patients. The most common (≥15%) adverse events occurring in pediatric patients are presented in Table 7.

Table 7: Adverse Reactions Occurring in at Least 15% of Patients Less than 18 Years of Age Enrolled in Study C09-001r

	Number (%) of Patients			
	< 2 yrs (n=5)	2 to < 12 yrs (n=10)	12 to <18 yrs (n=4)	Total (n=19)
General Disorders and Administration Site Conditions				
Pyrexia	4 (80)	4 (40)	1 (25)	9 (47)
Gastrointestinal Disorders				
Diarrhea	1 (20)	4 (40)	1 (25)	6 (32)
Vomiting	2 (40)	1 (10)	1 (25)	4 (21)
Infections and Infestations				
Upper respiratory tract infection[a]	2 (40)	3 (30)	1 (25)	6 (32)

	Number (%) of Patients			
	< 2 yrs (n=5)	2 to < 12 yrs (n=10)	12 to <18 yrs (n=4)	Total (n=19)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	3 (60)	2 (20)	0 (0)	5 (26)
Nasal congestion	2 (40)	2 (20)	0 (0)	4 (21)
Cardiac Disorders				
Tachycardia	2 (40)	2 (20)	0 (0)	4 (21)

[a] includes the preferred terms upper respiratory tract infection and nasopharyngitis.

Generalized Myasthenia Gravis (gMG)

In a 26-week placebo-controlled trial evaluating the effect of Soliris for the treatment of gMG (gMG Study 1), 62 patients received Soliris at the recommended dosage regimen and 63 patients received placebo. Patients were 19 to 79 years of age, and 66% were female. Table 8 displays the most common adverse reactions from gMG Study 1 that occurred in ≥5% of Soliris-treated patients and at a greater frequency than placebo.

Table 8: Adverse Reactions Reported in 5% or More of Soliris-Treated Patients in gMG Study 1 and at a Greater Frequency than in Placebo-Treated Patients

Adverse Reaction	Soliris (N=62) n (%)	Placebo (N=63) n (%)
Gastrointestinal Disorders		
Abdominal pain	5 (8)	3 (5)
General Disorders and Administration Site Conditions		
Peripheral edema	5 (8)	3 (5)
Pyrexia	4 (7)	2 (3)
Infections and Infestations		
Herpes simplex virus infections	5 (8)	1 (2)

Adverse Reaction	Soliris (N=62) n (%)	Placebo (N=63) n (%)
Injury, Poisoning, and Procedural Complications		
Contusion	5(8)	2(3)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	9 (15)	5 (8)

The most common adverse reactions (≥10%) that occurred in Soliris-treated patients in the long-term extension to gMG Study 1, Study ECU-MG-302, that are not included in Table 8 were headache (26%), nasopharyngitis (24%), diarrhea (15%), arthralgia (12%), upper respiratory tract infection (11%), and nausea (10%).

6.2 Immunogenicity

As with all proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to eculizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of Soliris has been evaluated using two different immunoassays for the detection of anti-eculizumab antibodies: a direct enzyme-linked immunosorbent assay (ELISA) using the Fab fragment of eculizumab as target was used for the PNH indication; and an electro-chemiluminescence (ECL) bridging assay using the eculizumab whole molecule as target was used for the aHUS indication, as well as for additional patients with PNH. In the PNH population, antibodies to Soliris were detected in 3/196 (2%) patients using the ELISA assay and in 5/161 (3%) patients using the ECL assay. In the aHUS population, antibodies to Soliris were detected in 3/100 (3%) patients using the ECL assay. An ECL based neutralizing assay with a low sensitivity of 2 mcg/mL was performed to detect neutralizing antibodies for the 3 patients with aHUS and the 5

patients with PNH with positive samples using the ECL assay. Two of 161 patients with PNH (1.2%) and 1 of 100 patients with aHUS (1%) had low positive values for neutralizing antibodies. None of 62 patients with gMG had antibodies to Soliris detected immediately following the 26-week active treatment.

No apparent correlation of antibody development to clinical response was observed.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Soliris. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Soliris exposure.

Cases of serious or fatal meningococcal infections have been reported.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

Alexion's PNH and aHUS disease registries collect pregnancy outcomes in women exposed to Soliris during pregnancy. To enroll or to obtain information, contact www.pnhregistry.com or www.ahusregistry.com, or call (215)-616-3558. In cases where gMG patients become pregnant, call (215)-616-3558.

Risk Summary

There are no available data on Soliris use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Soliris, a recombinant IgG molecule (humanized anti-C5 antibody), is expected to cross the placenta. Animal studies using a mouse analogue of the Soliris molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and moribund offspring at doses 2-8 times the human dose. Advise pregnant women of the potential risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Animal reproduction studies were conducted in mice using doses of a murine anti-C5 antibody that approximated 2-4 times (low dose) and 4-8 times (high dose) the recommended human Soliris dose, based on a body weight comparison. When animal exposure to the antibody occurred in the time period from before mating until early gestation, no decrease in fertility or reproductive performance was observed. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose; however, the exposure did not increase fetal loss or neonatal death. When maternal exposure to the antibody occurred in the time period from implantation through weaning, a higher number of male offspring became moribund or died (1/25 controls, 2/25 low dose group, 5/25 high dose group). Surviving offspring had normal development and reproductive function.

8.2 Lactation

Risk Summary

There is no information regarding the presence of eculizumab in human milk, the effects on the breastfed infant, or the effects on milk production. IgG is excreted in human milk, so it is expected that eculizumab will be present in human milk. However, published data suggest that antibodies in human milk do not enter the neonatal and infant circulation in substantial amounts. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Soliris and any potential adverse effects on the breastfed child from Soliris or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of Soliris for the treatment of PNH in pediatric patients have not been established.

The safety and effectiveness of Soliris for the treatment of aHUS have been established in pediatric patients. Use of Soliris in pediatric patients for this indication is supported by evidence from four adequate and well-controlled clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS. The studies included a total of 47 pediatric patients (ages 2 months to 17 years). The safety and effectiveness of Soliris for the treatment of aHUS appear similar in pediatric and adult patients [*see Adverse Reactions (6.1), and Clinical Studies (14.2)*].

The safety and effectiveness of Soliris for the treatment of generalized Myasthenia Gravis in pediatric patients have not been established.

Administer vaccinations for the prevention of infection due to *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib) according to ACIP guidelines [*see Warnings and Precautions (5.1, 5.2, 5.3)*].

8.5 Geriatric Use

Forty-five patients 65 years of age or older (15 with PNH, 4 with aHUS, and 26 with gMG) were treated with Soliris in clinical trials in the approved indications. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

11 DESCRIPTION

Soliris, a complement inhibitor, is a formulation of eculizumab which is a recombinant humanized monoclonal IgG2/4$_\kappa$ antibody produced by murine myeloma cell culture and purified by standard bioprocess technology. Eculizumab contains human constant regions from human IgG2 sequences and human IgG4 sequences and murine complementarity-determining regions grafted onto the 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.

Soliris is a sterile, clear, colorless, preservative-free 10 mg/mL solution for intravenous infusion and is supplied in 30-mL single-dose vials. The product is formulated at pH 7 and each vial contains 300 mg of eculizumab, 13.8 mg sodium phosphate monobasic, 53.4 mg sodium phosphate dibasic, 263.1 mg sodium chloride, 6.6 mg polysorbate 80 (vegetable origin) and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eculizumab, the active ingredient in Soliris, is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9.

Soliris inhibits terminal complement-mediated intravascular hemolysis in PNH patients and complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS.

The precise mechanism by which eculizumab exerts its therapeutic effect in gMG patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.

12.2 Pharmacodynamics

In the placebo-controlled clinical study (PNH Study 1), Soliris when administered as recommended reduced serum LDH levels from 2200 ± 1034 U/L (mean ± SD) at baseline to 700 ± 388 U/L by week one and maintained the effect through the end of the study at week 26 (327 ± 433 U/L) in patients with PNH. In the single arm clinical study (PNH Study 2), the effect was maintained through week 52 [*see Clinical Studies (14)*].

In patients with PNH, aHUS, and gMG, free C5 concentrations of < 0.5 mcg/mL was correlated with complete blockade of terminal complement activity.

12.3 Pharmacokinetics

Following intravenous maintenance doses of 900 mg once every 2 weeks in patients with PNH, the week 26 observed mean ± SD serum eculizumab maximum concentration (C_{max}) was 194 ± 76 mcg/mL and the trough concentration (C_{trough}) was 97 ± 60 mcg/mL. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with aHUS, the week 26 observed mean ± SD C_{trough} was 242 ± 101 mcg/mL. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with gMG, the week 26 observed mean ± SD C_{max} was 783 ± 288 mcg/mL and the C_{trough} was 341 ± 172 mcg/mL.

Steady state was achieved 4 weeks after starting eculizumab treatment, with accumulation ratio of approximately 2-fold in all studied indications. Population pharmacokinetic analyses showed that eculizumab pharmacokinetics were dose-linear and time-independent over the 600 mg to 1200 mg dose range, with inter-individual variability of 21% to 38%.

Distribution

The eculizumab volume of distribution for a typical 70 kg patient was 5 L to 8 L.

Elimination

The half-life of eculizumab was approximately 270 h to 375 h.

Plasma exchange or infusion increased the clearance of eculizumab by approximately 250-fold and reduced the half-life to 1.26 h. Supplemental dosing is recommended when Soliris is administered to patients receiving plasma exchange or infusion [*see Dosage and Administration (2. 4)*].

Specific Populations

Age, Sex, and Race:

The pharmacokinetics of eculizumab were not affected by age (2 months to 85 years), sex, or race.

Renal Impairment:

Renal function did not affect the pharmacokinetics of eculizumab in PNH (creatinine clearance of 8 mL/min to 396 mL/min calculated using Cockcroft-Gault formula), aHUS (estimated glomerular filtration rate [eGFR] of 5 mL/min/1.73 m^2 to105 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease [MDRD] formula), or gMG patients (eGFR of 44 mL/min/1.73 m^2 to 168 mL/min/1.73 m^2 using MDRD formula).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies of eculizumab have not been conducted.

Genotoxicity studies have not been conducted with eculizumab.

Effects of eculizumab upon fertility have not been studied in animals. Intravenous injections of male and female mice with a murine anti-C5 antibody at up to 4-8 times the equivalent of the clinical dose of Soliris had no adverse effects on mating or fertility.

14 CLINICAL STUDIES

14.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

The safety and efficacy of Soliris in PNH patients with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26 week study (PNH Study 1, NCT00122330); PNH patients were also treated with Soliris in a single arm 52 week study (PNH Study 2, NCT00122304) and in a long-term extension study (E05-001, NCT00122317). Patients received meningococcal vaccination prior to receipt of Soliris. In all studies, the dose of Soliris was 600 mg study drug every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration. Soliris was administered as an intravenous infusion over 25 - 45 minutes.

PNH Study 1:

PNH patients with at least four transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100,000/microliter were randomized to either Soliris (n = 43) or placebo (n = 44). Prior to randomization, all patients underwent an initial observation period to confirm the need for RBC transfusion

and to identify the hemoglobin concentration (the "set-point") which would define each patient's hemoglobin stabilization and transfusion outcomes. The hemoglobin set-point was less than or equal to 9 g/dL in patients with symptoms and was less than or equal to 7 g/dL in patients without symptoms. Endpoints related to hemolysis included the numbers of patients achieving hemoglobin stabilization, the number of RBC units transfused, fatigue, and health-related quality of life. To achieve a designation of hemoglobin stabilization, a patient had to maintain a hemoglobin concentration above the hemoglobin set-point and avoid any RBC transfusion for the entire 26 week period. Hemolysis was monitored mainly by the measurement of serum LDH levels, and the proportion of PNH RBCs was monitored by flow cytometry. Patients receiving anticoagulants and systemic corticosteroids at baseline continued these medications.

Major baseline characteristics were balanced (see Table 9).

Table 9: PNH Study1 Patient Baseline Characteristics

Parameter	Study 1	
	Placebo N = 44	Soliris N = 43
Mean age (SD)	38 (13)	42 (16)
Gender - female (%)	29 (66)	23 (54)
History of aplastic anemia or myelodysplastic syndrome (%)	12 (27)	8 (19)
Patients with history of thrombosis (events)	8 (11)	9 (16)
Concomitant anticoagulants (%)	20 (46)	24 (56)
Concomitant steroids/immunosuppressant treatments (%)	16 (36)	14 (33)
Packed RBC units transfused per patient in previous 12 months (median (Q1,Q3))	17 (14, 25)	18 (12, 24)
Mean Hgb level (g/dL) at setpoint (SD)	8 (1)	8 (1)
Pre-treatment LDH levels (median, U/L)	2,234	2,032
Free hemoglobin at baseline (median, mg/dL)	46	41

Patients treated with Soliris had significantly reduced ($p < 0.001$) hemolysis resulting in improvements in anemia as indicated by increased hemoglobin stabilization and reduced need for RBC transfusions compared to placebo treated patients (see Table 10). These

effects were seen among patients within each of the three pre-study RBC transfusion strata (4 - 14 units; 15 - 25 units; > 25 units). After 3 weeks of Soliris treatment, patients reported less fatigue and improved health-related quality of life. Because of the study sample size and duration, the effects of Soliris on thrombotic events could not be determined.

Table 10: PNH Study 1Results

	Placebo N = 44	Soliris N = 43
Percentage of patients with stabilized hemoglobin levels	0	49
Packed RBC units transfused per patient (median)	10	0
(range)	(2 - 21)	(0 - 16)
Transfusion avoidance (%)	0	51
LDH levels at end of study (median, U/L)	2,167	239
Free hemoglobin at end of study (median, mg/dL)	62	5

PNH Study 2 and Extension Study :

PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter received Soliris over a 52-week period. Concomitant medications included anti-thrombotic agents in 63% of the patients and systemic corticosteroids in 40% of the patients. Overall, 96 of the 97 enrolled patients completed the study (one patient died following a thrombotic event). A reduction in intravascular hemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in a reduced need for RBC transfusion and less fatigue. 187 Soliris-treated PNH patients were enrolled in a long term extension study. All patients sustained a reduction in intravascular hemolysis over a total Soliris exposure time ranging from 10 to 54 months. There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment. However, the majority of patients received concomitant anticoagulants; the effects of anticoagulant withdrawal during Soliris therapy was not studied [*see Warnings and Precautions (5.4)*].

14.2 Atypical Hemolytic Uremic Syndrome (aHUS)

Five single-arm studies [four prospective: C08-002A/B (NCT00844545 and NCT00844844), C08-003A/B (NCT00838513 and NCT00844428), C10-003 (NCT01193348), and C10-004 (NCT01194973); and one retrospective: C09-001r (NCT01770951)] evaluated the safety and efficacy of Soliris for the treatment of aHUS. Patients with aHUS received meningococcal vaccination prior to receipt of Soliris or received prophylactic treatment with antibiotics until 2 weeks after vaccination. In all studies, the dose of Soliris in adult and adolescent patients was 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg 7 ± 2 days later, then 1200 mg every 14 ± 2 days thereafter. The dosage regimen for pediatric patients weighing less than 40 kg enrolled in Study C09-001r and Study C10-003 was based on body weight [*see Dosage and Administration (2.2)*]. Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints.

Endpoints related to TMA included the following:

- platelet count change from baseline
- hematologic normalization *(maintenance of normal platelet counts and LDH levels for at least four weeks)*
- complete TMA response *(hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of four weeks)*
- TMA-event free status *(absence for at least 12 weeks of a decrease in platelet count of >25% from baseline, plasma exchange or plasma infusion, and new dialysis requirement)*
- Daily TMA intervention rate *(defined as the number of plasma exchange or plasma infusion interventions and the number of new dialyses required per patient per day).*

aHUS Resistant to PE/PI (Study C08-002A/B)

Study C08-002A/B enrolled patients who displayed signs of thrombotic microangiopathy (TMA) despite receiving at least four PE/PI treatments the week prior to screening. One patient had no PE/PI the week prior to screening because of PE/PI intolerance. In order to qualify for enrollment, patients were required to have a platelet count $\leq 150 \times 10^9$/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median patient age was 28 (range: 17 to 68 years). Patients enrolled in Study C08-002A/B were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 70%-121%. Seventy-six percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 11 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C08-002A/B.

Table 11: Baseline Characteristics of Patients Enrolled in Study C08-002A/B

Parameter	C08-002A/B N = 17
Time from aHUS diagnosis until screening in months, median (min, max)	10 (0.26, 236)
Time from current clinical TMA manifestation until screening in months, median (min, max)	<1 (<1, 4)
Baseline platelet count ($\times 10^9$/L), median (range)	118 (62, 161)
Baseline LDH (U/L), median (range)	269 (134, 634)

Patients in Study C08-002A/B received Soliris for a minimum of 26 weeks. In Study C08-002A/B, the median duration of Soliris therapy was approximately 100 weeks (range: 2 weeks to 145 weeks).

Renal function, as measured by eGFR, was improved and maintained during Soliris therapy. The mean eGFR (± SD) increased from 23 ± 15 mL/min/1.73m^2 at baseline to 56 ± 40 mL/min/1.73m^2 by 26 weeks; this effect was maintained through 2 years (56 ± 30 mL/min/1.73m^2). Four of the five patients who required dialysis at baseline were able to discontinue dialysis.

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In Study C08-002A/B, mean platelet count (± SD) increased from 109 ± 32 x10^9/L at baseline to 169 ± 72 x10^9/L by one week; this effect was maintained through 26 weeks (210 ± 68 x10^9/L), and 2 years (205 ± 46 x10^9/L). When treatment was continued for more than 26 weeks, two additional patients achieved Hematologic Normalization as well as Complete TMA response. Hematologic Normalization and Complete TMA response were maintained by all responders. In Study C08-002A/B, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Table 12 summarizes the efficacy results for Study C08-002A/B.

Table 12: Efficacy Results for Study C08-002A/B

Efficacy Parameter	aHUS Study 1 at 26 wks[1] N = 17	aHUS Study 1 at 2 yrs[2] N = 17
Complete TMA response, n (%)	11 (65)	13 (77)
Median Duration of complete TMA response, weeks (range)	38 (25, 56)	99 (25, 139)

Efficacy Parameter	aHUS Study 1 at 26 wks[1] N = 17	aHUS Study 1 at 2 yrs[2] N = 17
eGFR improvement ≥15 mL/min/1.73 m^2, n (%) Median duration of eGFR improvement, days (range)	9 (53) 251 (70, 392)	10 (59) ND
Hematologic normalization, n (%) Median Duration of hematologic normalization, weeks (range)	13 (76) 37 (25, 62)	15 (88) 99 (25, 145)
TMA event-free status, n (%)	15 (88)	15 (88)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 0.82 (0.04, 1.52) 0 (0, 0.31)	 0.82 (0.04, 1.52) 0 (0, 0.36)

[1] At data cut-off (September 8, 2010).
[2] At data cut-off (April 20, 2012).

aHUS Sensitive to PE/PI (Study C08-003A/B)

Study C08-003A/B enrolled patients undergoing chronic PE/PI who generally did not display hematologic signs of ongoing thrombotic microangiopathy (TMA). All patients had received PT at least once every two weeks, but no more than three times per week, for a minimum of eight weeks prior to the first Soliris dose. Patients on chronic dialysis were permitted to enroll in Study C08-003A/B. The median patient age was 28 years (range: 13 to 63 years). Patients enrolled in Study C08-003A/B were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 37%-118%. Seventy percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 13 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C08-003A/B.

Table 13: Baseline Characteristics of Patients Enrolled in Study C08-003A/B

Parameter	Study C08-003A/B N = 20
Time from aHUS diagnosis until screening in months, median (min, max)	48 (0.66, 286)
Time from current clinical TMA manifestation until screening in months, median (min, max)	9 (1, 45)
Baseline platelet count ($\times 10^9$/L), median (range)	218 (105, 421)
Baseline LDH (U/L), median (range)	200 (151, 391)

Patients in Study C08-003A/B received Soliris for a minimum of 26 weeks. In Study C08-003A/B, the median duration of Soliris therapy was approximately 114 weeks (range: 26 to 129 weeks).

Renal function, as measured by eGFR, was maintained during Soliris therapy. The mean eGFR (± SD) was 31 ± 19 mL/min/1.73m^2 at baseline, and was maintained through 26 weeks (37 ± 21 mL/min/1.73m^2) and 2 years (40 ± 18 mL/min/1.73m^2). No patient required new dialysis with Soliris.

Reduction in terminal complement activity was observed in all patients after the commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/PI. The mean platelet count (± SD) was 228 ± 78 x 10^9/L at baseline, 233 ± 69 x 10^9/L at week 26, and 224 ± 52 x 10^9/L at 2 years. When treatment was continued for more than 26 weeks, six additional patients achieved Complete TMA response. Complete TMA Response and Hematologic Normalization were maintained by all responders. In Study C08-003A/B, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Table 14 summarizes the efficacy results for Study C08-003A/B.

Table 14: Efficacy Results for Study C08-003A/B

Efficacy Parameter	Study C08-003A/Bat 26 wks[1] N = 20	Study C08-003A/B at 2 yrs[2] N = 20
Complete TMA response, n (%) Median duration of complete TMA response, weeks (range)	5 (25) 32 (12, 38)	11 (55) 68 (38, 109)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%)	1 (5)	8 (40)
TMA Event-free status n (%)	16 (80)	19 (95)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 0.23 (0.05, 1.07) 0	 0.23 (0.05, 1.07) 0 (0, 0.01)
Hematologic normalization[4], n (%) Median duration of hematologic normalization, weeks (range)[3]	18 (90) 38 (22, 52)	18 (90) 114 (33, 125)

[1] At data cut-off (September 8, 2010).
[2] At data cut-off (April 20, 2012).
[3] Calculated at each post-dose day of measurement (excluding Days 1 to 4) using a repeated measurement ANOVA model.
[4] In Study C08-003A/B, 85% of patients had normal platelet counts and 80% of patients had normal serum LDH levels at baseline, so hematologic normalization in this population reflects maintenance of normal parameters in the absence of PE/PI.

Retrospective Study in Patients with aHUS (C09-001r)

The efficacy results for the aHUS retrospective study (Study C09-001r) were generally consistent with results of the two prospective studies. Soliris reduced signs of

complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline. Mean platelet count (± SD) increased from 171 ± 83 $x10^9$/L at baseline to 233 ±109 $x10^9$/L after one week of therapy; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 254 ± 79 $x10^9$/L).

A total of 19 pediatric patients (ages 2 months to 17 years) received Soliris in Study C09-001r. The median duration of Soliris therapy was 16 weeks (range 4 to 70 weeks) for children <2 years of age (n=5), 31 weeks (range 19 to 63 weeks) for children 2 to <12 years of age (n=10), and 38 weeks (range 1 to 69 weeks) for patients 12 to <18 years of age (n=4). Fifty three percent of pediatric patients had an identified complement regulatory factor mutation or auto-antibody.

Overall, the efficacy results for these pediatric patients appeared consistent with what was observed in patients enrolled in Studies C08-002A/B and C08-003A/B (Table 15). No pediatric patient required new dialysis during treatment with Soliris.

Table 15: Efficacy Results in Pediatric Patients Enrolled in aHUS Study 3

Efficacy Parameter	<2 yrs (n=5)	2 to <12 yrs (n=10)	12 to <18 yrs (n=4)	Total (n=19)
Complete TMA response, n (%)	2 (40)	5 (50)	1 (25)	8 (42)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m^2, n (%)[2]	2 (40)	6 (60)	1 (25)	9 (47)
Platelet count normalization, n (%)[1]	4 (80)	10 (100)	3 (75)	17 (89)
Hematologic Normalization, n (%)	2 (40)	5 (50)	1 (25)	8 (42)
Daily TMA intervention rate, median (range)				
Before eculizumab	1 (0, 2)	<1 (0.07, 1.46)	<1 (0, 1)	0.31 (0.00, 2.38)
On eculizumab treatment	<1 (0, <1)	0 (0, <1)	0 (0, <1)	0.00 (0.00 , 0.08)

[1] Platelet count normalization was defined as a platelet count of at least 150,000 X 10^9/L on at least two consecutive measurements spanning a period of at least 4 weeks.
[2] Of the 9 patients who experienced an eGFR improvement of at least 15 mL/min/1.73 m^2, one received dialysis throughout the study period and another received Soliris as prophylaxis following renal allograft transplantation.

Adult Patients with aHUS (Study C10-004)

Study C10-004 enrolled patients who displayed signs of thrombotic microangiopathy (TMA). In order to qualify for enrollment, patients were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for

chronic dialysis. The median patient age was 35 (range: 18 to 80 years). All patients enrolled in Study C10-004 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 28%-116%. Fifty-one percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 35 patients received PE/PI prior to eculizumab. Table 16 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-004.

Table 16: Baseline Characteristics of Patients Enrolled in Study C10-004

Parameter	Study C10-004 N = 41
Time from aHUS diagnosis until start of study drug in months, median (range)	0.79 (0.03 – 311)
Time from current clinical TMA manifestation until first study dose in months, median (range)	0.52 (0.03-19)
Baseline platelet count ($\times 10^9$/L), median (range)	125 (16 – 332)
Baseline LDH (U/L), median (range)	375 (131 – 3318)

Patients in Study C10-004 received Soliris for a minimum of 26 weeks. In Study C10-004, the median duration of Soliris therapy was approximately 50 weeks (range: 13 weeks to 86 weeks).

Renal function, as measured by eGFR, was improved during Soliris therapy. The mean eGFR (± SD) increased from 17 ± 12 mL/min/1.73m^2 at baseline to 47 ± 24 mL/min/1.73m^2 by 26 weeks. Twenty of the 24 patients who required dialysis at study baseline were able to discontinue dialysis during Soliris treatment.

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Study C10-004, mean platelet count (± SD) increased from 119 ± 66 x10^9/L at baseline to 200 ± 84 x10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 252 ± 70 x10^9/L). In Study C10-004, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 17 summarizes the efficacy results for Study C10-004.

Table 17: Efficacy Results for Study C10-004

Efficacy Parameter	Study C10-004aHUS (N = 41)
Complete TMA response, n (%), 95% CI Median duration of complete TMA response, weeks (range)	23 (56), 40,72 42 (6, 75)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m2, n (%)	22 (54)
Hematologic Normalization, n (%) Median duration of hematologic normalization, weeks (range)	36 (88) 46 (10, 75)
TMA Event-free Status, n (%)	37 (90)
Daily TMA Intervention Rate, median (range) Before eculizumab On eculizumab treatment	 0.63 (0, 1.38) 0 (0, 0.58)

Pediatric and Adolescent Patients with aHUS (Study C10-003)

Study C10-003 enrolled patients who were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH above the upper limits of normal, serum creatinine level ≥97 percentile for age without the need for chronic dialysis. The median patient age was 6.5 (range: 5 months to 17 years). Patients enrolled in Study C10-003were required to have ADAMTS13 activity level above 5%;observed range of values in the trial were 38%-121%. Fifty percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 10 patients received PE/PI prior to eculizumab. Table 18 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-003.

Table 18: Baseline Characteristics of Patients Enrolled in aHUS Study 5

Parameter	Patients 1 month to <12 years (N = 18)	All Patients (N = 22)
Time from aHUS diagnosis until start of study drug in months, median (range)	0.51 (0.03 – 58)	0.56 (0.03-191)
Time from current clinical TMA manifestation until first study dose in months, median (range)	0.23 (0.03 – 4)	0.2 (0.03-4)
Baseline platelet count (x 10^9/L), median (range)	110 (19-146)	91 (19-146)
Baseline LDH (U/L) median (range)	1510 (282-7164)	1244 (282-7164)

Patients in Study C10-003 received Soliris for a minimum of 26 weeks. In Study C10-003, the median duration of Soliris therapy was approximately 44 weeks (range: 1 dose to 88 weeks).

Renal function, as measured by eGFR, was improved during Soliris therapy. The mean eGFR (± SD) increased from 33 ± 30 mL/min/1.73m^2 at baseline to 98 ± 44 mL/min/1.73m^2 by 26 weeks. Among the 20 patients with a CKD stage ≥2 at baseline, 17 (85%) achieved a CKD improvement of ≥1 stage. Among the 16 patients ages 1 month to <12 years with a CKD stage ≥2 at baseline, 14 (88%) achieved a CKD improvement by ≥1 stage. Nine of the 11 patients who required dialysis at study baseline were able to discontinue dialysis during Soliris treatment. Responses were observed across all ages from 5 months to 17 years of age.

Reduction in terminal complement activity was observed in all patients after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. The mean platelet count (± SD) increased from 88 ± 42 x10^9/L at baseline to 281 ± 123 x10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (±SD) at week 26: 293 ± 106 x10^9/L). In Study C10-003, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 19 summarizes the efficacy results for Study C10-003.

Table 19: Efficacy Results for Study C10-003

Efficacy Parameter	Patients 1 month to <12 years (N = 18)	All Patients (N = 22)
Complete TMA response, n (%) 95% CI Median Duration of complete TMA response, weeks (range)[1]	11 (61) 36, 83 40 (14, 77)	14 (64) 41, 83 37 (14, 77)
eGFR improvement ≥15 mL/min/ 1.73•m^2•n (%)	16 (89)	19 (86)
Complete Hematologic Normalization, n (%) Median Duration of complete hematologic normalization, weeks (range)	14 (78) 38 (14, 77)	18 (82) 38 (14, 77)
TMA Event-Free Status, n (%)	17 (94)	21 (95)
Daily TMA Intervention rate, median (range) Before eculizumab treatment On eculizumab treatment	0.2 (0, 1.7) 0 (0, 0.01)	0.4 (0, 1.7) 0 (0, 0.01)

[1] through data cutoff (October 12, 2012).

14.3 Generalized Myasthenia Gravis (gMG)

The efficacy of Soliris for the treatment of gMG was established in gMG Study 1 (NCT01997229), a 26-week randomized, double-blind, parallel-group, placebo-controlled, multicenter trial that enrolled patients who met the following criteria at screening:

1. Positive serologic test for anti-AChR antibodies,
2. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV,
3. MG-Activities of Daily Living (MG-ADL) total score ≥6,
4. Failed treatment over 1 year or more with 2 or more immunosuppressive therapies (ISTs) either in combination or as monotherapy, or failed at least 1 IST and required chronic plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (IVIg).

A total of 62 patients were randomized to receive Soliris treatment and 63 were randomized to receive placebo. Baseline characteristics were similar between treatment groups, including age at diagnosis (38 years in each group), gender [66% female (eculizumab) versus 65% female (placebo)], and duration of gMG [9.9 (eculizumab) versus 9.2 (placebo) years]. Over 95% of patients in each group were receiving acetylcholinesterase (AchE) inhibitors, and 98% were receiving immunosuppressant

therapies (ISTs). Approximately 50% of each group had been previously treated with at least 3 ISTs.

Soliris was administered according to the recommended dosage regimen [*see Dosage and Administration (2.3)*].

The primary efficacy endpoint for gMG Study 1 was a comparison of the change from baseline between treatment groups in the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) total score at Week 26. The MG-ADL is a categorical scale that assesses the impact on daily function of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function (total score 0-24). A statistically significant difference favoring Soliris was observed in the mean change from baseline to Week 26 in MG-ADL total scores [-4.2 points in the Soliris-treated group compared with -2.3 points in the placebo-treated group (p=0.006)].

A key secondary endpoint in gMG Study 1 was the change from baseline in the Quantitative Myasthenia Gravis (QMG) total score at Week 26. The QMG is a 13-item categorical scale assessing muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness (total score 0-39). A statistically significant difference favoring Soliris was observed in the mean change from baseline to Week 26 in QMG total scores [-4.6 points in the Soliris-treated group compared with -1.6 points in the placebo-treated group (p=0.001)].

The results of the analysis of the MG-ADL and QMG from gMG Study 1are shown in Table 20.

Table 20: Analysis of Change from Baseline to Week 26 in MG-ADL and QMG Total Scores in gMG Study 1

Efficacy Endpoints	Soliris-LS Mean (n=62) (SEM)	Placebo-LS Mean (n=63) (SEM)	Soliris change relative to placebo – LS Mean Difference (95% CI)	p-values
MG-ADL	-4.2 (0.49)	-2.3 (0.48)	-1.9 (-3.3, -0.6)	(0.006[a]; 0.014[b])
QMG	-4.6 (0.60)	-1.6 (0.59)	-3.0 (-4.6, -1.3)	(0.001 [a]; 0.005 [b])

SEM= Standard Error of the Mean;

Soliris-LSMean = least square mean for the treatment group;

Placebo-LSMean = least square mean for the placebo group;

LSMean-Difference (95% CI) = Difference in least square mean with 95% confidence interval;

p-values (testing the null hypothesis that there is no difference between the two treatment arms a: in least square means at Week 26 using a repeated measure analysis; b: in ranks at Week 26 using a worst rank analysis).

In gMG Study 1, a clinical response was defined in the MG-ADL total score as at least a 3-point improvement and in QMG total score as at least a 5-point improvement. The proportion of clinical responders at Week 26 with no rescue therapy was statistically significantly higher for Soliris compared to placebo for both measures. For both endpoints, and also at higher response thresholds (≥4-, 5-, 6-, 7-, or 8-point improvement on MG-ADL, and ≥6-, 7-, 8-, 9-, or 10-point improvement on QMG), the proportion of clinical responders was consistently greater for Soliris compared to placebo. Available data suggest that clinical response is usually achieved by 12 weeks of Soliris treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

Soliris (eculizumab) is supplied as 300 mg single-dose vials containing 30 mL of 10 mg/mL sterile, preservative-free Soliris solution per vial.

Store Soliris vials in the original carton until time of use under refrigerated conditions at 2-8º C (36-46º F) and protected from light. Soliris vials may be held in the original carton at controlled room temperature (not more than 25° C/77° F) for only a single period up to 3 days. Do not use beyond the expiration date stamped on the carton. Refer to *Dosage and Administration (2)*) for information on the stability and storage of diluted solutions of Soliris.

DO NOT FREEZE. DO NOT SHAKE.

NDC 25682-001-01 Single unit 300 mg carton: Contains one (1) 30 mL vial of Soliris (10 mg/mL).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Medication Guide).

Meningococcal Infection

Prior to treatment, patients should fully understand the risks and benefits of Soliris, in particular the risk of meningococcal infection. Ensure that patients receive the Medication Guide.

Inform patients that they are required to receive meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris, if they have not previously been vaccinated. They are required to be revaccinated according to current medical guidelines for meningococcal vaccines use while on Soliris therapy. Inform patients that vaccination may not prevent meningococcal infection *[see Warnings and Precautions (5.1)]*.

Signs and Symptoms of Meningococcal Infection

Inform patients about the signs and symptoms of meningococcal infection, and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms are as follows:

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Inform patients that they will be given a Soliris Patient Safety Information Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

Other Infections

Inform patients that there may be an increased risk of other types of infections, particularly those due to encapsulated bacteria. Additionally, Aspergillus infections have occurred in immunocompromised and neutropenic patients. Inform parents or caregivers of children receiving Soliris for the treatment of aHUS that their child should be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib) according to current medical guidelines.

Discontinuation

Inform patients with PNH that they may develop hemolysis due to PNH when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 8 weeks following Soliris discontinuation.

Inform patients with aHUS that there is a potential for TMA complications due to aHUS when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 12 weeks following Soliris discontinuation. Inform patients who discontinue Soliris to keep the Soliris Patient Safety Information Card with them for three months after the last Soliris dose, because the increased risk of meningococcal infection persists for several weeks following discontinuation of Soliris.

Manufactured by:

Alexion Pharmaceuticals, Inc.
100 College Street
New Haven, CT 06510 USA

US License Number 1743

This product, or its use, may be covered by one or more US patents, including US Patent No. 6,355,245 in addition to others including patents pending.

MEDICATION GUIDE
SOLIRIS® (so-leer-is)
(eculizumab)
injection, for intravenous use

What is the most important information I should know about SOLIRIS?

SOLIRIS is a medicine that affects your immune system. SOLIRIS can lower the ability of your immune system to fight infections.

- **SOLIRIS increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.**

1. You must receive meningococcal vaccines at least 2 weeks before your first dose of SOLIRIS unless you have already had this vaccine. If your doctor decided that urgent treatment with SOLIRIS is needed, you should receive meningococcal vaccination as soon as possible.

2. If you had a meningococcal vaccine in the past, you might need additional vaccination before starting SOLIRIS. Your doctor will decide if you need additional meningococcal vaccination.

3. Meningococcal vaccines do not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:

- headache with nausea or vomiting
- headache with a stiff neck or stiff back
- fever and a rash
- muscle aches with flu-like symptoms
- headache and a fever
- fever
- confusion
- eyes sensitive to light

Your doctor will give you a Patient Safety Card about the risk of meningococcal infection. Carry it with you at all times during treatment and for 3 months after your last SOLIRIS dose. Your risk of meningococcal infection may continue for several weeks after your last dose of SOLIRIS. It is important to show this card to any doctor or nurse who treats you. This will help them diagnose and treat you quickly.

SOLIRIS is only available through a program called the SOLIRIS REMS. Before you can receive SOLIRIS, your doctor must:

- enroll in the SOLIRIS REMS program
- counsel you about the risk of meningococcal infection
- give you information about the symptoms of meningococcal infection
- give you a **Patient Safety Card** about your risk of meningococcal infection, as discussed above
- make sure that you are vaccinated with a meningococcal vaccine

SOLIRIS may also increase the risk of other types of serious infections. If your child is treated with SOLIRIS, make sure that your child receives vaccinations against Streptococcus pneumoniae and Haemophilis influenza type b (Hib).

What is SOLIRIS?

SOLIRIS is a prescription medicine called a monoclonal antibody. SOLIRIS is used to treat:

- adults with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH)
- adults and children with a disease called atypical Hemolytic Uremic Syndrome (aHUS)
- adults with a disease called generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive

It is not known if SOLIRIS is safe and effective in children with PNH or gMG.

Who should not receive SOLIRIS?

Do not receive SOLIRIS if you:

- have a meningococcal infection.
- have not been vaccinated against meningitis infection unless your doctor decides that urgent treatment with SOLIRIS is needed. See "What is the most important information I should know about SOLIRIS?"

Before you receive SOLIRIS, tell your doctor about all of your medical conditions, including if you:

- have an infection or fever.
- are pregnant or plan to become pregnant. It is not known if SOLIRIS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SOLIRIS passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. SOLIRIS and other medicines can affect each other causing side effects.

It is important that you:

- have all recommended vaccinations before you start SOLIRIS.
- stay up-to-date with all recommended vaccinations during treatment with SOLIRIS.

Know the medications you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I receive SOLIRIS?

- SOLIRIS is given through a vein (I.V. or intravenous infusion) usually over 35 minutes in adults and 1 to 4 hours in pediatric patients. If you have an allergic reaction during your SOLIRIS infusion, your doctor may decide to give SOLIRIS more slowly or stop your infusion.
- If you are an adult, you will usually receive a SOLIRIS infusion by your doctor:
  - weekly for five weeks, then
  - every 2 weeks

- If you are less than 18 years of age, your doctor will decide how often you will receive SOLIRIS depending on your age and body weight
- After each infusion, you should be monitored for one hour for allergic reactions. See "What are the possible side effects of SOLIRIS?"
- If you forget or miss a SOLIRIS infusion, call your doctor right away.
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping SOLIRIS. Stopping treatment with SOLIRIS may cause breakdown of your red blood cells due to PNH.**
  Symptoms or problems that can happen due to red blood cell breakdown include:
  - drop in the number of your red blood cell count
  - drop in your platelet count
  - confusion
  - chest pain
  - difficulty breathing
  - kidney problems
  - blood clots
- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

Symptoms or problems that can happen with abnormal clotting may include:
- stroke
- confusion
- seizures
- chest pain (angina)
- difficulty breathing
- kidney problems
- swelling in arms or legs
- a drop in your platelet count

What are the possible side effects of SOLIRIS?
SOLIRIS can cause serious side effects including:
- See **"What is the most important information I should know about SOLIRIS?"**
- **Serious allergic reactions.** Serious allergic reactions can happen during your SOLIRIS infusion. Tell your doctor or nurse right away if you get any of these symptoms during your SOLIRIS infusion:
  - chest pain
  - trouble breathing or shortness of breath
  - swelling of your face, tongue, or throat
  - feel faint or pass out

If you have an allergic reaction to SOLIRIS, your doctor may need to infuse SOLIRIS more slowly, or stop SOLIRIS. See "How will I receive SOLIRIS?"

The most common side effects in people with PNH treated with SOLIRIS include:
- headache
- back pain
- pain or swelling of your nose or throat (nasopharyngitis)
- nausea

The most common side effects in people with aHUS treated with SOLIRIS include:
- headache
- abdominal pain
- cough
- fever
- diarrhea
- vomiting
- swelling of legs or feet (peripheral edema)
- hypertension
- pain or swelling of your nose or throat (nasopharyngitis)
- nausea
- common cold (upper respiratory infection)
- anemia
- urinary tract infections

The most common side effects in people with gMG treated with SOLIRIS include:
- muscle and joint (musculoskeletal) pain

Tell your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects of SOLIRIS. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of SOLIRIS.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SOLIRIS for a condition for which it was not prescribed. Do not give SOLIRIS to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about SOLIRIS that is written for health professionals.

What are the ingredients in SOLIRIS?
Active ingredient: eculizumab
Inactive ingredients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80 (vegetable origin) and Water for Injection
Manufactured by Alexion Pharmaceuticals, Inc., 100 College Street, New Haven, CT 06510 USA.

Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 10/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166Orig1s422

REMS

Initial REMS Approval: 6/2010
Most Recent Modification: 10/2017

BLA 125166 SOLIRIS® (ECULIZUMAB)

RECOMBINANT HUMANIZED MONOCLONAL ANTIBODY

Alexion Pharmaceuticals, Inc.

100 College Street

New Haven, CT 06510

(475) 230-2596

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S)

The goals of the REMS are:

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To educate Healthcare Professionals (HCPs) and Patients regarding:
  - the increased risk of meningococcal infections with Soliris
  - the early signs of invasive meningococcal infections, and
  - the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections

II. REMS ELEMENTS

A. Medication Guide

Alexion will ensure that a Medication Guide is dispensed with each prescription of Soliris and in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

B. Elements to Assure Safe Use

Healthcare providers who prescribe Soliris are certified.

a. Prescriber certification is based on prescriber agreement that the prescriber must:

   i) Counsel patients and provide the patient educational materials to the patient, including the Soliris Patient Safety Card and the Medication Guide

   ii) Provide the Medication Guide to the patient prior to each infusion

   iii) Review the educational materials (Soliris Patient Safety Card, Prescriber Introductory Letter, Prescriber Safety Brochure *Important Safety Information about Soliris,* Patient Safety Brochure *Important Safety Information about Soliris,* and Dosing and Administration Guide) and the product labeling and comply with the directions for safe use including ensuring patients receive a meningococcal vaccine.

iv) Promptly report to Alexion at 1-844-259-6783 or to the FDA at 1-800-332-1088 or 1-800-300-43874 (serious life-threatening) cases of meningococcal infection, including the patients' clinical outcomes

b. The prescriber must fax the completed enrollment form to 1-877-580-2596 (ALXN), email the completed form to OSSP@alxn.com, or mail the form to Alexion Pharmaceuticals, Inc.; Attn: OneSource Safety Support Program; 100 College Street, New Haven, CT 06510. A prescriber may also complete the enrollment by phone with Alexion at 1-888-765-4747 or obtain enrollment documents via the Soliris REMS website at www.solirisrems.com. A prescriber may also complete the enrollment on the internet via the Soliris REMS-dedicated website at www.solirisrems.com.

c. Alexion must contact certified prescribers every year to provide the educational materials (Medication Guide, Soliris Patient Safety Card, Prescriber Safety Brochure, *and Important Safety Information about Soliris,* Patient Safety Brochure, *Important Safety Information about Soliris,* and Dosing and Administration Guide). The educational materials and enrollment form will also be available on a REMS-dedicated webpage at www.solirisrems.com. The REMS-dedicated website (www.solirisrems.com) will be accessible directly or from a link from www.soliris.net.

d. The following materials are part of the REMS and are appended

(1) Soliris Patient Safety Card

(2) Prescriber Introductory Letter and Enrollment Form

(3) Patient Safety Brochure, *Important Safety Information about Soliris*

(4) Prescriber Safety Brochure, *Important Safety Information about Soliris*

(5) Dosing and Administration Guide

(6) Soliris REMS website (www.solirisrems.com)

e. Alexion must maintain a database of certified prescribers in the REMS program, and will ensure that Soliris is distributed only to certified prescribers. Alexion must ensure that prescribers comply with the requirements of the REMS Program.

C. Timetable for Submission of Assessments

REMS assessments must be submitted to the FDA every two years beginning June 1, 2015. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that

assessment. Alexion will submit each assessment so that it will be received by the FDA on or before the due date.

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MEDICATION GUIDE
SOLIRIS® (so-leer-is)
(eculizumab)
injection, for intravenous use

What is the most important information I should know about SOLIRIS?

SOLIRIS is a medicine that affects your immune system. SOLIRIS can lower the ability of your immune system to fight infections.

- **SOLIRIS increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.**

1. You must receive meningococcal vaccines at least 2 weeks before your first dose of SOLIRIS unless you have already had this vaccine. If your doctor decided that urgent treatment with SOLIRIS is needed, you should receive meningococcal vaccination as soon as possible.

2. If you had a meningococcal vaccine in the past, you might need additional vaccination before starting SOLIRIS. Your doctor will decide if you need additional meningococcal vaccination.

3. Meningococcal vaccines do not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:

- headache with nausea or vomiting
- headache with a stiff neck or stiff back
- fever and a rash
- muscle aches with flu-like symptoms
- headache and a fever
- fever
- confusion
- eyes sensitive to light

Your doctor will give you a Patient Safety Card about the risk of meningococcal infection. Carry it with you at all times during treatment and for 3 months after your last SOLIRIS dose. Your risk of meningococcal infection may continue for several weeks after your last dose of SOLIRIS. It is important to show this card to any doctor or nurse who treats you. This will help them diagnose and treat you quickly.

SOLIRIS is only available through a program called the SOLIRIS REMS. Before you can receive SOLIRIS, your doctor must:

- enroll in the SOLIRIS REMS program
- counsel you about the risk of meningococcal infection
- give you information about the symptoms of meningococcal infection
- give you a **Patient Safety Card** about your risk of meningococcal infection, as discussed above
- make sure that you are vaccinated with a meningococcal vaccine

SOLIRIS may also increase the risk of other types of serious infections. If your child is treated with SOLIRIS, make sure that your child receives vaccinations against Streptococcus pneumoniae and Haemophilis influenza type b (Hib).

What is SOLIRIS?

SOLIRIS is a prescription medicine called a monoclonal antibody. SOLIRIS is used to treat:

- adults with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH)
- adults and children with a disease called atypical Hemolytic Uremic Syndrome (aHUS)
- adults with a disease called generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive

It is not known if SOLIRIS is safe and effective in children with PNH or gMG.

Who should not receive SOLIRIS?

Do not receive SOLIRIS if you:

- have a meningococcal infection.
- have not been vaccinated against meningitis infection unless your doctor decides that urgent treatment with SOLIRIS is needed. See "What is the most important information I should know about SOLIRIS?"

Before you receive SOLIRIS, tell your doctor about all of your medical conditions, including if you:

- have an infection or fever.
- are pregnant or plan to become pregnant. It is not known if SOLIRIS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SOLIRIS passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. SOLIRIS and other medicines can affect each other causing side effects.

It is important that you:

- have all recommended vaccinations before you start SOLIRIS.
- stay up-to-date with all recommended vaccinations during treatment with SOLIRIS.

Know the medications you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I receive SOLIRIS?

- SOLIRIS is given through a vein (I.V. or intravenous infusion) usually over 35 minutes in adults and 1 to 4 hours in pediatric patients. If you have an allergic reaction during your SOLIRIS infusion, your doctor may decide to give SOLIRIS more slowly or stop your infusion.
- If you are an adult, you will usually receive a SOLIRIS infusion by your doctor:
  - weekly for five weeks, then
  - every 2 weeks

- If you are less than 18 years of age, your doctor will decide how often you will receive SOLIRIS depending on your age and body weight
- After each infusion, you should be monitored for one hour for allergic reactions. See "What are the possible side effects of SOLIRIS?"
- If you forget or miss a SOLIRIS infusion, call your doctor right away.
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping SOLIRIS. Stopping treatment with SOLIRIS may cause breakdown of your red blood cells due to PNH.**
  Symptoms or problems that can happen due to red blood cell breakdown include:
  - drop in the number of your red blood cell count
  - drop in your platelet count
  - confusion
  - chest pain
  - difficulty breathing
  - kidney problems
  - blood clots
- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

Symptoms or problems that can happen with abnormal clotting may include:
- stroke
- confusion
- seizures
- chest pain (angina)
- difficulty breathing
- kidney problems
- swelling in arms or legs
- a drop in your platelet count

What are the possible side effects of SOLIRIS?
SOLIRIS can cause serious side effects including:
- See **"What is the most important information I should know about SOLIRIS?"**
- **Serious allergic reactions.** Serious allergic reactions can happen during your SOLIRIS infusion. Tell your doctor or nurse right away if you get any of these symptoms during your SOLIRIS infusion:
  - chest pain
  - trouble breathing or shortness of breath
  - swelling of your face, tongue, or throat
  - feel faint or pass out

If you have an allergic reaction to SOLIRIS, your doctor may need to infuse SOLIRIS more slowly, or stop SOLIRIS. See "How will I receive SOLIRIS?"

The most common side effects in people with PNH treated with SOLIRIS include:
- headache
- pain or swelling of your nose or throat (nasopharyngitis)
- back pain
- nausea

The most common side effects in people with aHUS treated with SOLIRIS include:
- headache
- abdominal pain
- cough
- fever
- diarrhea
- vomiting
- swelling of legs or feet (peripheral edema)
- hypertension
- pain or swelling of your nose or throat (nasopharyngitis)
- nausea
- common cold (upper respiratory infection)
- anemia
- urinary tract infections

The most common side effects in people with gMG treated with SOLIRIS include:
- muscle and joint (musculoskeletal) pain

Tell your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects of SOLIRIS. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of SOLIRIS.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SOLIRIS for a condition for which it was not prescribed. Do not give SOLIRIS to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about SOLIRIS that is written for health professionals.

What are the ingredients in SOLIRIS?
Active ingredient: eculizumab
Inactive ingredients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80 (vegetable origin) and Water for Injection
Manufactured by Alexion Pharmaceuticals, Inc., 100 College Street, New Haven, CT 06510 USA.

Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 10/2017

PATIENT SAFETY INFORMATION CARD

Important Safety Information for Patients Taking Soliris®

Soliris can lower the ability of your immune system to fight infections, **especially meningococcal infection, which requires immediate medical attention.** If you experience any of the following symptoms, you should immediately call your doctor or seek emergency medical care, preferably in a major emergency medical care center:

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Get emergency medical care right away if you have any of these signs or symptoms and show this card.

Even if you stop using Soliris, keep this card with you for 3 months after your last Soliris dose. Your risk of meningococcal infection may continue for several weeks after your last dose of Soliris.

PATIENT SAFETY INFORMATION CARD

Information for the Treating Physician

This patient has been prescribed Soliris® (eculizumab) therapy, which increases the patient's susceptibility to meningococcal infection *(Neisseria meningitidis)* **or other general infections.**

- Meningococcal infections may be rapidly life-threatening or fatal if not recognized and treated early
- **Evaluate immediately if infection is suspected and treat with appropriate antibiotics if necessary**
- Contact prescribing physician (below) as soon as possible

For more information about Soliris, please refer to the full Prescribing Information or call **1.888.SOLIRIS (1.888.765.4747).** In case of adverse event experiences, call **1.844.259.6783.**

Patients receiving Soliris should carry this card at all times. Show this card to any doctor involved in your health care.

Patient Name _____

Prescriber Name _____

Prescriber Number _____

SOLIRIS®
(eculizumab)

Dear Soliris® (eculizumab) Prescriber,

Alexion, the maker of Soliris, would like to notify you of a Risk Evaluation and Mitigation Strategy (REMS) called the OneSource Safety Support Program (OSSP) to provide important safety information about Soliris.

To get started in the Program, please complete the Prescriber Enrollment Form on the reverse side. The completed Prescriber Enrollment Form can be faxed to the Soliris OneSource Safety Support Program (OSSP) at 1.877.580.2596 (ALXN); scanned and e-mailed to OSSP@alxn.com; or mailed to Alexion Pharmaceuticals, Inc., Attn: OneSource Safety Support Program; *100 College Street, New Haven, CT 06510. Enrollment can also be completed online at www.solirisrems.com.*

I have received the Soliris educational materials provided through the Soliris OneSource Safety Support Program and I have reviewed information about:

- The need for the patient to receive meningococcal vaccination at least 2 weeks prior to beginning Soliris (eculizumab), unless the risk of delaying Soliris therapy outweighs the risk of developing meningococcal infection
- The risks of developing meningococcal infection while receiving Soliris (eculizumab)

I agree to:

- Review the product labeling and educational materials, and comply with the safety instructions for use, including ensuring meningococcal vaccination status
- Counsel patients (or caregivers, or legal guardians) and provide educational materials to the patient (or caregivers, or legal guardians), including the Soliris Patient Safety Information Card, and the Soliris Medication Guide
- Intend to promptly report cases of meningococcal infection, including the patient's clinical outcomes, by contacting Alexion Pharmaceuticals, Inc., (OneSource Safety Support Program) at 1.844.259.6783 or reporting the information to the FDA MedWatch Reporting System by phone at 1.800.FDA.1088 (1.800.332.1088) or by mail using Form 3500 at www.fda.gov/medwatch
- Revaccinate patients in accordance with the Advisory Committee on Immunization Practices (ACIP) recommendations for the duration of Soliris therapy

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. [See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of meningococcal infection].
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

Please complete enrollment form on the reverse side of this letter.

INDICATIONS AND USAGE

Soliris is a complement inhibitor indicated for:

- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.
- The treatment patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.
- The treatment of patients with generalized Myasthenia Gravis (gMG) who are anti-Acetylcholine Receptor (AchR) antibody positive.

Limitation of Use

Soliris is not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).

CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved *Neisseria meningitidis* infection.
- Patients who are not currently vaccinated against *Neisseria meningitidis,* unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection.

WARNINGS AND PRECAUTIONS

- Discontinue Soliris in patients who are being treated for serious meningococcal infections.
- Use caution when administering Soliris to patients with any other systemic infection.

ADVERSE REACTIONS

- The most frequently reported adverse reactions in the PNH randomized trials (≥10% overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea.
- The most frequently reported adverse reactions in aHUS single arm prospective trials (≥20% combined per patient incidence) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections, and pyrexia.
- The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial (≥10% and greater than placebo) is: musculoskeletal pain.

Please see full prescribing information for Soliris (eculizumab), including boxed WARNING regarding serious meningococcal infection.

I acknowledge that I have read the above information and agree to comply with the conditions listed when treating a patient with Soliris.

Name (printed):_____

Signature: _____Date: _____ Title:_____

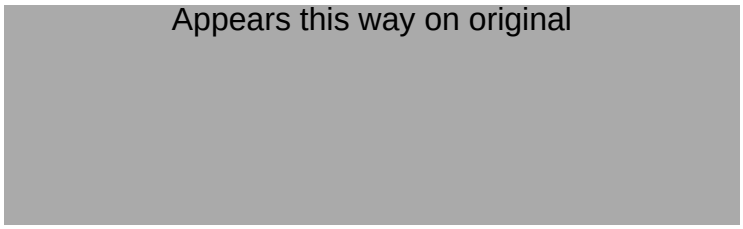
Office Address: _____ E-mail:_____

City:_____ State:_____ ZIP:_____

Country:_____ Phone Number:_____ Fax Number:_____

BEFORE STARTING YOUR PATIENTS ON SOLIRIS®

Important safety information for the healthcare provider



Prior to initiating Soliris® (eculizumab) therapy, it's important to review with patients the *Soliris Patient Safety Information Card* and instruct them to be diligent and follow the safety information. Encourage your patients to ask any questions they may have about Soliris at any time. Your patients will come to you for the answers, so provide them with the best education and support you can by becoming better acquainted with Soliris safety information.

These tools are to aid you in your discussions. In our ongoing effort to maximize the safety and improve outcomes we have provided safety resources, including:

- Patient Safety Information Card
- A Soliris Medication Guide for you and your patients

Please see back cover for Important Safety Information.

Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.

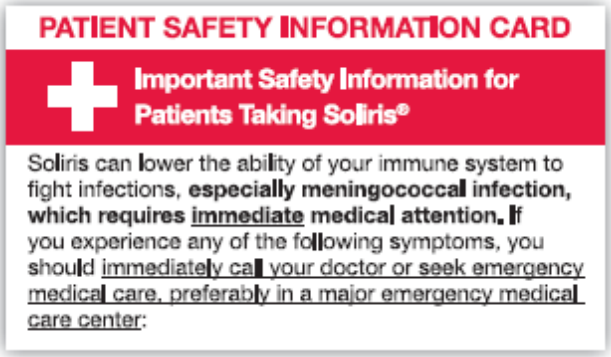
Patient Safety Information Card

You are provided with Patient Safety Information Cards to give to your patients. You should discuss the importance and the proper use of this card with every patient. Patients should carry this card at all times to show to any healthcare professional involved in their care. The Patient Safety Information Card contains safety guidance for Soliris patients and their healthcare providers.

Prescribers should advise patients to seek medical attention immediately if

they develop headache with nausea or vomiting, or headache and fever, even

if they don't have their Patient Safety Information Card with them.



PATIENT SAFETY INFORMATION CARD

Important Safety Information for Patients Taking Soliris®

Soliris can lower the ability of your immune system to fight infections, **especially meningococcal infection, which requires immediate medical attention. If** you experience any of the following symptoms, you should immediately call your doctor or seek emergency medical care, preferably in a major emergency medical care center:

For Discussion with Patients—Important Safety Information

MEDICATION GUIDE

Soliris® (so-leer-is)

(eculizumab)

Read the Medication Guide before you start Soliris and before each infusion. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment. Talk to your doctor if you have any questions about your treatment with Soliris.

What is the most important information I should know about Soliris?

Soliris is a medicine that affects your immune system. Soliris can lower the ability of your immune system to fight infections.

- **Soliris increases your chance of getting serious and life-threatening meningococcal infections**

Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.

- **You must receive meningococcal vaccination at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decided that urgent treatment with Soliris is needed, you should receive meningococcal vaccination as soon as possible.**

- **If you had a meningococcal vaccine in the past, you might need additional vaccination before starting Soliris. Your doctor will decide if you need additional meningococcal vaccination.**
- **Meningococcal vaccines do not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:**

  — headache with nausea or vomiting

  — headache and a fever

  — headache with a stiff neck or stiff back

  — fever

  — fever and a rash

  — confusion

  — muscle aches with flu-like symptoms

  — eyes sensitive to light

Your doctor will give you a **Patient Safety Card** about the risk of meningococcal infection. Carry it with you at all times during treatment and for 3 months after your last Soliris® dose. Your risk of meningococcal infection may continue for several weeks after your last dose of Soliris. It is important to show this card to any doctor or nurse who treats you. This will help them diagnose and treat you quickly.

Soliris is only available through a program called the Soliris REMS. Before you can receive Soliris, your doctor must:

- enroll in the Soliris REMS program
- counsel you about the risk of meningococcal infection
- give you information about the symptoms of meningococcal infection
- give you a **Patient Safety Card** about your risk of meningococcal infection, as discussed above.
- make sure that you are vaccinated with a meningococcal vaccine

Soliris may also increase the risk of other types of serious infections. If your

child is treated with Soliris, make sure that your child receives vaccinations

against *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib).

What is Soliris?

Soliris is a prescription medicine called a monoclonal antibody. Soliris is used to treat people with:

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH)..
- a disease called atypical Hemolytic Uremic Syndrome (aHUS)..
- a disease called generalized Myasthenia Gravis (gMG).

Soliris works by blocking part of your immune system. This can help your symptoms but it can also increase your chance for infection.

It is important that you:

- have all recommended vaccinations before you start Soliris
- stay up-to-date with all recommended vaccinations during treatment with Soliris

For Discussion with Patients—Important Safety Information (continued)

Who should not receive Soliris®?

Do not receive Soliris if you:

- have a meningococcal infection
- have not been vaccinated against meningitis infection, unless your doctor decides that urgent treatment with Soliris is needed. See “What is the most important information I should know about Soliris?”

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if, you:

- have an infection or fever
- are pregnant or plan to become pregnant. It is not known if Soliris will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Soliris passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes in adults and 1-4 hours in pediatric patients. If you have an allergic reaction during your Soliris infusion, your doctor may decide to give Soliris more slowly or stop your infusion.
- If you are an adult, you will usually receive a Soliris infusion by your doctor:
  — weekly for five weeks, then

  — every 2 weeks

- If you are less than 18 years of age, your doctor will decide how often you will receive Soliris depending on your age and body weight.
- After each infusion, you should be monitored for one hour for allergic reactions. See “What are the possible side effects of Soliris?”
- If you forget or miss a Soliris infusion, call your doctor right away.

- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris®. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**
  Symptoms or problems that can happen due to red blood cell breakdown include:
  — drop in the number of your red blood cell count

  — drop in your platelet count

  — confusion

  — chest pain

  — kidney problems

  — blood clots

  — difficulty breathing

- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**
  Symptoms or problems that can happen with abnormal clotting may include:
  — stroke

  — confusion

  — seizures

  — chest pain (angina)

  — difficulty breathing

  — kidney problems

— swelling in arms or legs

— a drop in your platelet count

•

What are the possible side effects of Soliris?

Soliris can cause serious side effects, including:

- **See “What is the most important information I should know about Soliris?”**
- Serious allergic reactions. Serious allergic reactions can happen during your Soliris infusion. Tell your doctor or nurse right away if you get any of these symptoms during your Soliris infusion:
  — chest pain

  — trouble breathing or shortness of breath

  — swelling of your face, tongue, or throat

  — feel faint or pass out

If you have an allergic reaction to Soliris, your doctor may need to infuse Soliris more slowly, or stop Soliris. See “How will I receive Soliris?”

For Discussion with Patients—Important Safety Information (continued)

Common side effects in people with PNH treated with Soliris® include:

- headaches
- runny nose and colds
- sore throat
- back pain
- nausea

Common side effects in people with aHUS treated with Soliris include:

- headache
- diarrhea
- high blood pressure
- common cold (upper respiratory infection)
- abdominal pain
- vomiting
- nasopharyngitis
- low red blood cell count
- cough
- peripheral edema
- nausea
- urinary tract infection
- pyrexia

Common side effects in people with gMG treated with Soliris include:

- muscle and joint (musculoskeletal) pain

Tell your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects of Soliris. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1.800.FDA.1088.

Please see back cover for Important Safety Information.

Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.

Appears this way on original

General information about Soliris®

Medicines are sometimes prescribed for conditions other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Soliris. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Soliris that is written for healthcare professionals.

What are the ingredients in Soliris?

Active ingredient: eculizumab

Inactive ingredients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80 (vegetable origin) and Water for Injection.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by Alexion Pharmaceuticals, Inc.

100 College Street, New Haven, CT 06510 USA.

Revised: 10/2017

Want to learn more about Soliris®?

- Visit www.Soliris.net or www.solirisrems.com
- Call 1.888.SOLIRIS (1.888.765.4747) for information regarding Soliris and the Soliris REMS
- To report suspected Adverse Event experiences, please call Alexion Pharmaceuticals, Inc. at 1.844.259.6783

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection. [See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of meningococcal infection].
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea.

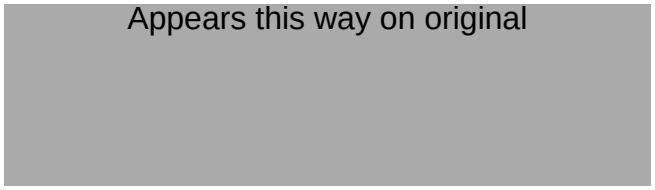
The most frequently reported adverse reactions in aHUS single arm prospective trials (≥20% combined per patient incidence) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections, and pyrexia.

The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial (≥10%) is: musculoskeletal pain.

Please see full Prescribing Information for Soliris, including boxed WARNING regarding serious meningococcal infection.

Before starting on Soliris®

Important safety information for patients



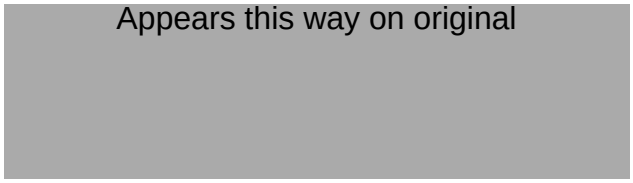
Before you begin Soliris® (eculizumab) treatment, your physician will give you a:

- Medication Guide
- Soliris Patient Safety Information Card

Read this information and ask your physician any questions you may have about Soliris at any time. Your physician will be able to provide you with the best education and support.

Please see back cover for Important Safety Information.

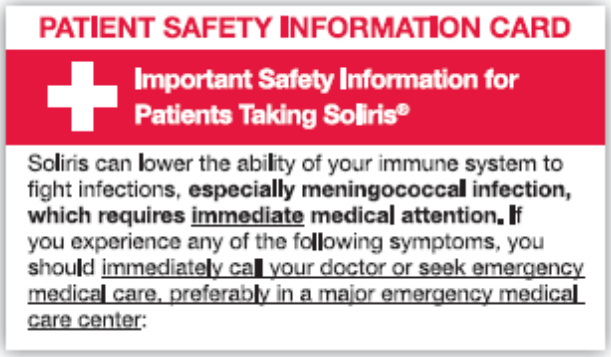
Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.



Patient Safety Information Card

You will receive a Patient Safety Information Card from your doctor that lists symptoms of a meningococcal infection and what to do if you have one. Your doctor should discuss with you the importance and the proper use of this card.

Carry this card at all times and show it to any healthcare professional who treats you. Seek immediate treatment for headache with nausea or vomiting, or headache with fever, even if you do not have your Patient Safety Information Card with you. Your Patient Safety Information Card contains safety guidance for you and your healthcare providers.


PATIENT SAFETY INFORMATION CARD

Important Safety Information for Patients Taking Soliris®

Soliris can lower the ability of your immune system to fight infections, **especially meningococcal infection, which requires immediate medical attention. If** you experience any of the following symptoms, you should immediately call your doctor or seek emergency medical care, preferably in a major emergency medical care center:

Soliris OneSource™ Treatment Support Program

Soliris OneSource is a program offered by Alexion that provides education; assistance with funding options and access to Soliris; and ongoing treatment support for people living with PNH, aHUS, or gMG and their caregivers. OneSource is staffed by Alexion Nurse Case Managers who are registered nurses with healthcare and insurance expertise. Alexion Pharmaceuticals developed this program to help make disease awareness and treatment access as easy as possible for you and your healthcare team.

Questions about PNH, aHUS, gMG or Soliris? Just call OneSource at 1.888.SOLIRIS (1.888.765.4747) to speak with an Alexion Nurse Case Manager.

For Discussion with Patients—Important Safety Information

MEDICATION GUIDE

Soliris® (so-leer-is)

(eculizumab)

Read the Medication Guide before you start Soliris and before each infusion. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment. Talk to your doctor if you have any questions about your treatment with Soliris.

What is the most important information I should know about Soliris?

Soliris is a medicine that affects your immune system. Soliris can lower the ability of your immune system to fight infections.

- **Soliris increases your chance of getting serious and life-threatening meningococcal infections**

Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.

- **You must receive meningococcal vaccination at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decided that urgent treatment with Soliris is needed, you should receive meningococcal vaccination as soon as possible.**
- **If you had a meningococcal vaccine in the past, you might need additional vaccination before starting Soliris. Your doctor will decide if you need additional meningococcal vaccination.**

- **Meningococcal vaccines do not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:**

  — headache with nausea or vomiting

  — headache and a fever

  — headache with a stiff neck or stiff back

  — fever

  — fever and a rash

  — confusion

  — muscle aches with flu-like symptoms

  — eyes sensitive to light

Your doctor will give you a **Patient Safety Card** about the risk of meningococcal infection. Carry it with you at all times during treatment and for 3 months after your last Soliris® dose. Your risk of meningococcal infection may continue for several weeks after your last dose of Soliris. It is important to show this card to any doctor or nurse who treats you. This will help them diagnose and treat you quickly.

Soliris is only available through a program called the Soliris REMS. Before you can receive Soliris, your doctor must:

- enroll in the Soliris REMS program
- counsel you about the risk of meningococcal infection
- give you information about the symptoms of meningococcal infection
- give you a **Patient Safety Card** about your risk of meningococcal infection, as discussed above.
- make sure that you are vaccinated with a meningococcal vaccine

Soliris may also increase the risk of other types of serious infections. If your

child is treated with Soliris, make sure that your child receives vaccinations

against *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib).

What is Soliris?

Soliris is a prescription medicine called a monoclonal antibody. Soliris is used to treat people with:

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH).
- a disease called atypical Hemolytic Uremic Syndrome (aHUS).
- a disease called generalized Myasthenia Gravis (gMG).

Soliris works by blocking part of your immune system. This can help your symptoms but it can also increase your chance for infection.

It is important that you:

- have all recommended vaccinations before you start Soliris
- stay up-to-date with all recommended vaccinations during treatment with Soliris

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Who should not receive Soliris®?

Do not receive Soliris if you:

- have a meningococcal infection
- have not been vaccinated against meningitis infection, unless your doctor decides that urgent treatment with Soliris is needed. See “What is the most important information I should know about Soliris?”

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if you:

- have an infection or fever
- are pregnant or plan to become pregnant. It is not known if Soliris will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Soliris passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes in adults and 1-4 hours in pediatric patients. If you have an allergic reaction during your Soliris infusion, your doctor may decide to give Soliris more slowly or stop your infusion.

- If you are an adult, you will usually receive a Soliris infusion by your doctor:
- — weekly for five weeks, then
- — every 2 weeks
- If you are less than 18 years of age, your doctor will decide how often you will receive Soliris depending on your age and body weight.
- After each infusion, you should be monitored for one hour for allergic reactions. See “What are the possible side effects of Soliris?”
- If you forget or miss a Soliris infusion, call your doctor right away.

Please see back cover for Important Safety Information.

Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.

- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris®. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**
  Symptoms or problems that can happen due to red blood cell breakdown include:
  — drop in the number of your red blood cell count

  — drop in your platelet count

  — confusion

  — chest pain

  — kidney problems

  — blood clots

  — difficulty breathing

- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**
  Symptoms or problems that can happen with abnormal clotting may include:
  — stroke

  — confusion

  — seizures

  — chest pain (angina)

  — difficulty breathing

  — kidney problems

  — swelling in arms or legs

  — a drop in your platelet count

•

What are the possible side effects of Soliris?

Soliris can cause serious side effects, including:

- **See "What is the most important information I should know about Soliris?"**
- Serious allergic reactions. Serious allergic reactions can happen during your Soliris infusion. Tell your doctor or nurse right away if you get any of these symptoms during your Soliris infusion:
  — chest pain

  — trouble breathing or shortness of breath

  — swelling of your face, tongue, or throat

  — feel faint or pass out

  If you have an allergic reaction to Soliris, your doctor may need to infuse Soliris more slowly, or stop Soliris. See "How will I receive Soliris?"

For Discussion with Patients—Important Safety Information (continued)

Common side effects in people with PNH treated with Soliris® include:

- headaches
- runny nose and colds
- sore throat
- back pain
- nausea

Common side effects in people with aHUS treated with Soliris include:

- headache
- diarrhea
- high blood pressure
- common cold (upper respiratory infection)
- abdominal pain
- vomiting
- nasopharyngitis
- low red blood cell count
- cough
- peripheral edema
- nausea
- urinary tract infection
- pyrexia

Common side effects in people with gMG treated with Soliris include:

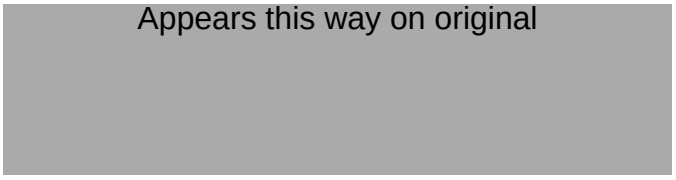
-
- ` muscle and joint (musculoskeletal) pain
-

Tell your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects of Soliris. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. To report any suspected adverse event experience, contact Alexion Pharmaceuticals Inc. at 1-844-259-6783 or report to the FDA at 1.800.FDA.1088.

Please see back cover for Important Safety Information.

Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.



General information about Soliris®

Medicines are sometimes prescribed for conditions other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Soliris. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Soliris that is written for healthcare professionals.

What are the ingredients in Soliris?

Active ingredient: eculizumab

Inactive ingredients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80 (vegetable origin) and Water for Injection.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by Alexion Pharmaceuticals, Inc.

100 College Street, New Haven, CT 06510 USA.

Revised: 10/2017

Want to learn more about Soliris®?

- Visit www.Soliris.net or www.solirisrems.com
- Call 1.888.SOLIRIS (1.888.765.4747) for information regarding Soliris and the Soliris REMS

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection. [See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of meningococcal infection].
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea.

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥20% combined per patient incidence) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections, and pyrexia.

The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial (≥10%) is:, musculoskeletal pain, ,

Please see full Prescribing Information for Soliris, including boxed WARNING regarding serious meningococcal infection.

PNH | aHUS | gMG

For Paroxysmal Nocturnal Hemoglobinuria (**PNH**), atypical Hemolytic Uremic Syndrome (**aHUS**), and generalized Myasthenia Gravis **(gMG)** patients

Dosing and Administration Guide

Soliris is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.

Soliris is indicated for the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement mediated thrombotic microangiopathy.

Limitation of Use

Soliris is not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).

Soliris is indicated for the treatment of patients with generalized Myasthenia Gravis (gMG) who are anti-Acetylcholine Receptor (AchR) antibody positive.

Please see enclosed full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infection.

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection. [See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of meningococcal infection].
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

Indications and usage

Soliris is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.

Soliris is indicated for the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

Limitation of Use

Soliris is not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).

The treatment of patients with generalized Myasthenia Gravis (gMG) who are anti-Acetylcholine Receptor (AchR) antibody positive.

Adverse reactions

The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea.

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥20% combined per patient incidence) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections and pyrexia.

The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial (≥10%) is: musculoskeletal pain. .

Please see enclosed full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infection.

To Report Suspected Adverse Event Experiences

Contact your healthcare provider. To report any suspected adverse event experience, contact Alexion Pharmaceuticals Inc. at 1.844.259.6783 or report to the FDA at 1.800.FDA.1088.

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For patients with **P**aroxysmal **N**octurnal **H**emoglobinuria (**PNH**)

Soliris® (eculizumab) PNH Dosing Guide

All patients must be vaccinated against *Neisseria meningitidis* at least 2 weeks prior to the first dose of Soliris therapy. Do not initiate Soliris therapy in patients with unresolved serious *Neisseria meningitidis* infection or who are not currently vaccinated, unless the risks of delaying Soliris treatment outweigh the risk of developing a meningococcal infection.[1]

Soliris: a chronic therapy for a chronic disease[1,2]

PNH Dosing Schedule for Patients >18 years

Pretreatment		Induction Phase				Maintenance Phase					
≥2 weeks before induction	Week	1	2	3	4	5	6	7	8	9+	q14d
Neisseria meningitidis vaccination	Soliris dose	600 mg	600 mg	600 mg	600 mg	900 mg	X	900 mg	X	900 mg	

Administer Soliris at the recommended dosage regimen time points, or within two days of these time points.

Administer Soliris at the recommended dosing interval or within 2 days before or after these time points.

- Fixed dose on time is critical to control chronic, complement-mediated hemolysis; for breakthrough hemolysis, dosing may be adjusted to every 12 days instead of 14 days[1]
- No dosing adjustments recommended based on age, gender, race, or renal insufficiency[1]
- Premedications are not routinely required

Monitoring after Discontinuation

Monitor patients after discontinuing Soliris for at least 8 weeks to detect hemolysis.

Important Administration Information

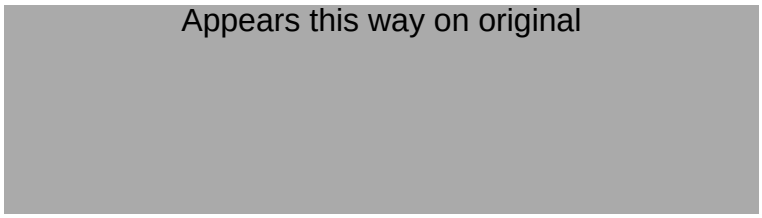
Dilute Soliris to a final admixture concentration of 5 mg/mL prior to administration.

The diluted solution is a clear, colorless liquid and should be practically free of any particles.

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

- If diluted solution is refrigerated, warm to room temperature (18°C-25°C [64°F-77°F]) only by exposure to ambient air
- Administer as an IV infusion over 35 minutes in adults and 1-4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump
- It is not necessary to protect diluted solution from light during administration

To learn more about Soliris, please call 1.888.SOLIRIS (1.888.765.4747) or visit www.Soliris.net. To learn more about Soliris REMS, please call 1.888.SOLIRIS (1.888.765.4747) or visit www.solirisrems.com.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For patients with **a**typical **H**emolytic **U**remic Syndrome (**aHUS**)

Soliris® (eculizumab) aHUS Dosing Guide

All patients must be vaccinated against *Neisseria meningitidis* at least 2 weeks prior to the first dose of Soliris therapy. Do not initiate Soliris therapy in patients with unresolved serious *Neisseria meningitidis* infection or who are not currently vaccinated, unless the risks of delaying Soliris treatment outweigh the risk of developing a meningococcal infection.[1]

Soliris is a therapy for aHUS—a chronic disease needing chronic treatment[1]

aHUS Adult (≥18 years of age) Dosing Schedule[1]

Pretreatment		Induction Phase				Maintenance Phase					
≥2 weeks before induction	Week	1	2	3	4	5	6	7	8	9+	q14d
Neisseria meningitidis vaccination	Soliris dose	900 mg	900 mg	900 mg	900 mg	1200 mg	—	1200 mg	—	1200 mg	

aHUS Weight-Based Dosing Schedule for Patients <18 Years[1]

Body Weight	Induction Phase	Maintenance Phase
40 kg and over	900 mg weekly × 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly × 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly × 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly × 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly × 1 dose	300 mg at week 2; then 300 mg every 3 weeks

Administer Soliris at the recommended dosing interval or within 2 days before or after these time points.

Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion[1]

Type of Plasma Intervention	Most Recent Soliris Dose	Supplemental Soliris Dose With Each Plasma Intervention	Timing of Supplemental Soliris Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	≥600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥300 mg	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

Monitoring after Discontinuation

Thrombotic microangiopathy (TMA) complications after discontinuation were observed in the aHUS clinical studies.[1]

aHUS patients who discontinue treatment with Soliris should be monitored closely for at least 12 weeks for signs and symptoms of TMA complications. If TMA complications occur after Soliris discontinuation, consider reinstitution of Soliris treatment, plasma therapy,[†] or appropriate organ-specific supportive measures.[1]

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

- If diluted solution is refrigerated, warm to room temperature (18°C-25°C [64°F-77°F]) only by exposure to ambient air
- Administer as an IV infusion over 35 minutes in adults and 1-4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump
- It is not necessary to protect diluted solution from light during administration

To learn more about Soliris, please call 1.888.SOLIRIS (1.888.765.4747) or visit www.Soliris.net. To learn more about Soliris REMS, please call 1.888.SOLIRIS (1.888.765.4747) or visit www.solirisrems.com.

[†]Plasma therapy = plasmapheresis, plasma exchange, or fresh frozen plasma infusion (PE/PI).

For patients with generalized Myasthenia Gravis (**gMG**)

Soliris® (eculizumab) gMG Dosing Guide

All patients must be vaccinated against *Neisseria meningitidis* at least 2 weeks prior to the first dose of Soliris therapy. Do not initiate Soliris therapy in patients with unresolved serious *Neisseria meningitidis* infection or who are not currently vaccinated, unless the risks of delaying Soliris treatment outweigh the risk of developing a meningococcal infection.[1]

Soliris is a therapy for gMG—a chronic disease needing chronic treatment[1]

Refractory gMG Adult (≥18 years of age) Dosing Schedule[1]

Pretreatment		Induction Phase				Maintenance Phase					
≥2 weeks before induction	Week	1	2	3	4	5	6	7	8	9+	q14d
Neisseria meningitidis vaccination	Soliris dose	900 mg	900 mg	900 mg	900 mg	1200 mg	—	1200 mg	—	1200 mg	

Administer Soliris at the recommended dosing interval or within 2 days before or after these time points.

Please see enclosed full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infection.

Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion[1]

Type of Plasma Intervention	Most Recent Soliris Dose	Supplemental Soliris Dose With Each Plasma Intervention	Timing of Supplemental Soliris Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	≥600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥300 mg	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

Use of Soliris in gMG treatment has been studied only in the setting of chronic administration.

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

- If diluted solution is refrigerated, warm to room temperature (18°C-25°C [64°F-77°F]) only by exposure to ambient air
- Administer as an IV infusion over 35 minutes in adults and 1-4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump
- It is not necessary to protect diluted solution from light during administration

To learn more about Soliris, please call 1.888.SOLIRIS (1.888.765.4747) or visit www.Soliris.net. To learn more about Soliris REMS, please call 1.888.SOLIRIS (1.888.765.4747) or visit www.solirisrems.com.

[†]Plasma therapy = plasmapheresis, plasma exchange, or fresh frozen plasma infusion (PE/PI).

For **PNH, aHUS and gMG**

Preparation of Soliris® (eculizumab) for Administration[1]

All patients must be vaccinated against *Neisseria meningitidis* at least 2 weeks prior to the first dose of Soliris therapy. Do not initiate Soliris therapy in patients with unresolved serious *Neisseria meningitidis* infection or who are not currently vaccinated, unless the risks of delaying Soliris treatment outweigh the risk of developing a meningococcal infection.[1]

Soliris Dose	Diluent Volume	Final Volume
300 mg	30 mL	30 mL
600 mg	60 mL	120 mL
900 mg	90 mL	180 mL
1200 mg	120 mL	240 mL

1. Withdraw the required amount of Soliris from the vial into a sterile syringe and transfer the recommended dose to an infusion bag.

2. Dilute Soliris to a final concentration of 5 mg/mL using the above table as a guideline. The volume of diluent should be equivalent to the drug volume.

3. Gently invert the infusion bag containing the diluted solution to ensure thorough mixture of the product and the diluent
    - Discard any unused portion left in the vial, as the product contains no preservatives.

4. Inspect visually for particulate matter and discoloration prior to administration
    - The diluted solution is a clear colorless liquid and should be practically free of any particles.

5. Allow the admixture to adjust to room temperature prior to administration (18°C-25°C, 64°F-77°F). **It must not be heated in a microwave or with any heat source other than ambient air temperature.**

6. Admixed solution of Soliris is stable for 24 hours at 2°C-8°C (36°F-46°F) and at room temperature.

Please see enclosed full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infection.

How Supplied, Storage, and Distribution[1]

- Vial—30 mL, liquid
- Product strength—10 mg/mL
- Product count—300 mg/30 mL (vial)
- Product physical specs—1 vial per carton
  — Shipped just in time for infusion
  — Weight: <1 lb
  — Dimensions: 1.625″ × 1.625″ × 3.125″
- Must be stored in the original carton until time of use under conditions at 2°C-8°C (36°F-46°F). Soliris vials may be held in the original carton at controlled room temperature (not more than 25° C/77° F) for only a single period up to 3 days.
- Protect from light
- DO NOT FREEZE; DO NOT SHAKE
- Do not infuse beyond the expiration date stamped on the carton
- NDC 25682-001-01: Each single-unit carton contains one 30-mL vial of Soliris (10 mg/mL)

To enroll in the Soliris REMS and order Soliris, please call 1.888.SOLIRIS (1.888.765.4747). To learn more about Soliris REMS, please call 1.888.SOLIRIS (1.888.765.4747) or visit solirisrems.com. The completed Prescriber Enrollment Form can be faxed to the Soliris OneSource Safety Support Program (OSSP) at 1.877.580.2596 (ALXN); scanned and e-mailed to OSSP@alxn.com; or mailed to Alexion Pharmaceuticals, Inc., 100 College Street, New Haven, CT 06510. Enrollment can also be completed online at solirisrems.com.

Contact Soliris OneSource at 1.888.SOLIRIS (1.888.765.4747)

- All Alexion Nurse Case Managers are registered nurses and have extensive insurance and clinical experience. An Alexion Nurse Care Manager will partner with each patient and his or her healthcare team
- Fast and convenient same-day shipping that meets the needs of PNH and aHUS patients

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection. [See *Warnings and Precautions* (5.1) for additional guidance on the management of the risk of meningococcal infection].
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

Please see enclosed full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infection.

References: **1**. Soliris® [package insert]. New Haven, CT. Alexion Pharmaceuticals, Inc. 2016 **2**. Helley D, de Latour RP, Porcher R, et al. French Society of Hematology. Evaluation of hemostasis and endothelial function in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. *Haematologica*. 2010;95:574-581.

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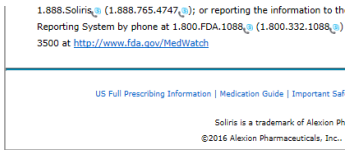
1.888.Soliris (1.888.765.4747); or reporting the information to th
Reporting System by phone at 1.800.FDA.1088 (1.800.332.1088)
3500 at http://www.fda.gov/MedWatch
US Full Prescribing Information | Medication Guide | Important Saf
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166Orig1s422

OFFICER/EMPLOYEE LIST

Officer/Employee List

Application: BLA 125166/s422
Soliris (eculizimab) injection

Indication: indicated for the treatment of patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor antibody (AchR) positive.

The following officers or employees of FDA participated in the decision to approve this application and consent to be identified:

Bilal AbuAsal
Cara Alfaro
Eric Bastings
Atul Bhattaram
Christopher Breder
Donella Fitzgerald
Andrea Franco
Brenda Gehrke
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Twanda Scales
Barbara Wilcox
Marcia Britt Williams
Sharon Williams

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166Orig1s422

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 14, 2017
From	Nick Kozauer, MD
Subject	Cross-Discipline Team Leader Review
BLA # (Supplement #)	125166 (422)
Applicant	Alexion Pharmaceuticals, Inc.
Date of Submission	December 23, 2016
PDUFA Goal Date	October 23, 2017
Proprietary Name / Non-Proprietary Name	Soliris/eculizumab
Dosage form(s)	Solution for intravenous injection
Strength(s)	900 mg weekly for 4 weeks, followed by 1200 mg for the next dose 1 week later and then every 2 weeks thereafter
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of subjects with gMG who are anti-AChR antibody positive

1. Background

This application contains data in support of the efficacy of eculizumab, administered as an intravenous (IV) injection, for the treatment of subjects with generalized myasthenia gravis (gMG) who are anti-acetylcholinesterase (anti-AChR) antibody positive. The applicant has proposed that the indication (b) (4) . Eculizumab has been FDA-approved under the trade name Soliris for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in 2007. Accelerated approval for the treatment of atypical hemolytic uremic syndrome (aHUS) was granted in 2011, with a conversion to a full approval in 2014.

MG is a chronic neuromuscular disorder that leads to varying degrees of skeletal muscle weakness most frequently in the eyes, face, neck, and limbs. This weakness generally worsens with activity and improves with rest. MG affecting multiple muscle groups is referred to as generalized MG. The disease is autoimmune in nature and results from the production of antibodies that, in most cases, attack post-synaptic nicotinic acetylcholine receptors at the neuromuscular junction. This damage then prevents nerve impulses from triggering muscle contractions. MG most commonly affects young adult females (under 40 years of age) and older adult males (over 60 years of age), but can occur at any age. The disease has a variable prognosis with many subjects responding well to treatment. However, approximately 30 percent of affected subjects can die within 7 years of diagnosis. Some subjects also experience myasthenic crises, which are episodes of severe weakness requiring emergency medical care for respiratory failure.

Eculizumab is a recombinant monoclonal antibody that binds to the complement protein C5, thereby inhibiting its cleavage to C5a and C5b, which prevents formation of the terminal complement complex C5b-9 (also termed the membrane attack complex [MAC]). Uncontrolled terminal complement activation is known to be involved in the destructive process at the neuromuscular junction in MG.

The only FDA-approved treatment for MG is pyridostigmine, an acetylcholinesterase inhibitor, which was approved in 1955 under the trade name Mestinon. A number of immunosuppressive therapies (ISTs) are used off-label to treat MG. Thymectomy is also used to treat some subjects with MG, especially (but not exclusively) the approximately 15% of subjects with a thymoma. Other treatments for MG in clinical practice that are either not subject to FDA regulation or not FDA-approved can include plasmapheresis, plasma exchange, and high-dose intravenous immune globulin (IVIg).

This application contains data from a 26-week randomized, double-blind, placebo-controlled trial as the primary basis of support for the effectiveness of eculizumab in gMG. Additional supportive information comes from the blinded transition period of the open-label extension phase of that trial, as well as an early-phase crossover trial.

The regulatory history of the development of eculizumab for the treatment of gMG is detailed in Dr. Christopher Breder's clinical review. The reader is referred there for additional information. This development program was granted orphan drug designation for the treatment of MG in 2014.

2. Product Quality

A review of the immunogenicity assays was conducted Dr. Andrea Franco, from the Office of Product Quality (OPQ). Dr. Joslyn Brunelle was the OPQ team lead for this application. The review notes that the screening and neutralizing antibody assays have limitations in their ability to detect low concentrations of anti-drug antibodies (ADA) because of high levels of drug found in the blood samples. The OPQ review comments, however, that the lack of a clinical safety signal or apparent loss of efficacy in the current development program (discussed later in this memo), as well as the lack of any known issues with ADA or neutralizing antibodies in the approved clinical indications, suggest a low risk for ADA development with this product.

3. Nonclinical Pharmacology/Toxicology

Not applicable.

4. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Atul Bhattaram, Dr. Kevin Krudys, and Dr. Sreedharan Sabarinath (the clinical pharmacology team lead).

A focus of the OCP review was an evaluation of the ability of the changes in the Myasthenia Gravis – Activities of Daily Living Scale (MG-ADL) from an early-phase crossover trial (Study C8-001) to support the effectiveness of eculizumab for the treatment of gMG. The OCP review also evaluated treatment-related reductions in free complement protein C5 concentrations in Study ECU-MG-301 (Study 301) as a supportive pharmacodynamic marker of efficacy. These analyses will be presented later in the efficacy section of this memo under a discussion of the results of the respective trials.

The OCP review also made recommendations for Section 12.3 of the Prescribing Information (PI) related to parameter estimates for clearance and volume of distribution. Proposed labeling statements by the applicant regarding the pharmacodynamic effects of eculizumab for Section 12.2 of the PI were also found to be acceptable.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

Dr. Christopher Breder was the clinical review for this application. Dr. Junshan Qui was the biometrics reviewer, and Dr. Hsien Ming (Jim) Hung was the biometrics Division Director for this application.

Study ECU-MG-301 (Study 301)

The following table, adapted based on the information in Dr. Breder's review, outlines the design of Study 301 which is intended as the main evidence in support of the effectiveness of eculizumab for the treatment of gMG.

Study 301					
Design	**Duration**	**Population**	**Sample Size**	**Dose**	**Primary Efficacy Endpoint**
Randomized, double-blind, placebo-controlled	26 weeks	Refractory gMG (age 18 years or older), with anti-AchR antibodies confirmed at screening. The criteria for being considered refractory are outlined in Dr. Breder's review and involve the failure of ISTs and/or the need for chronic plasmapheresis, PE, and/or IVIg.	Total n=125 (n=62 eculizumab and n=63 placebo). Subjects were stratified based on Myasthenia Gravis Foundation of America (MGFA) clinical criteria.	900 mg IV weekly for the first 4 doses, 1200 mg IV one week later, followed by 1200 mg IV every 2 weeks thereafter.	A worst-rank analysis using the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale.

The aspect of the analysis of the results of Study 301 that requires the most consideration relates to the development of the statistical analysis plan (SAP). A detailed history is provided in both Dr. Breder's and Dr. Qui's reviews.

The primary analysis of Study 301 was a worst-rank analysis of covariance (ANCOVA) with effects for treatment. This analysis utilized the Myasthenia Gravis – Activities of Daily Living (MG-ADL) scale which is an acceptable primary endpoint that assesses functional capabilities in MG patients. The scale evaluates functional capabilities across 8 domains that are each scored 0-3 (maximum score of 24), with worst scores indicating greater impairment (further details about the scale are provided in Dr. Breder's review). Essentially, this analysis "ranks" subjects in terms of their outcomes in the trial (based on MG-ADL score, death, discontinuation, and need for rescue therapy), and then compares these rankings between treatment arms.

During the development of the different versions of the SAP for Study 301, there had been discussion between the Division and the applicant with respect to the most appropriate approach to the hierarchy of the ranks to be used for the analysis. In Version 2 of the SAP, MG-ADL scores were ranked based on performance for all subjects not requiring rescue therapy. Subjects needing rescue therapy would be given lower ranks based on the time to rescue therapy from baseline (with the shortest times getting the worst ranks). The following strategy was proposed to handle subjects who dropped out before Week 26, but were not evaluated for the need for rescue therapy:

- Subjects in this group who had an MG crisis without rescue therapy would be assigned to the rescue therapy group. These ranks would be based on the time to the MG crisis from baseline.
- Subjects in this group who has a worsening to a score of 3 or a 2-point worsening on any of the individual MG-ADL items (excluding double vision or eyelid droop) without rescue therapy would be assigned to the rescue therapy group. These ranks would be based on the time to this degree of worsening from baseline.
- All other subjects who dropped out before Week 26 who didn't meet either of these preceding criteria would be ranked based on the last observation carried forward (LOCF) for the MG-ADL scores.

The Division did not object to this version of the SAP, but had asked some clarifying questions to the applicant, primarily with respect to various sensitivity analyses that might be informative. In response,

the applicant subsequently submitted Version 3 of the SAP. This version was based on a more conservative approach and indicated that subjects who died would get the worst ranks, with ranks based on the time to death from baseline. Subjects who had an MG crisis would receive the next worst ranks, based on the time to the MG crisis from baseline. Subjects needing rescue therapy, *as well as subjects who drop out for any reason without rescue therapy*, would be ranked next (after death and MG crisis) based on the time to rescue therapy or drop out from baseline. All other subjects who did not drop out or receive rescue therapy would be ranked based on their change from baseline in MG-ADL scores to Week 26 (or LOCF if Week 26 is missing). Version 3 of the SAP was in place at the time of the analysis of the data from Study 301.

The following table, copied from Dr. Qui's review, presents the results of the primary efficacy analysis based on Version 3 of the SAP.

Table 3-6 Change from Baseline in Myasthenia Gravis Activities of Daily Living Total Score at Week 26: (ANCOVA Worst –Rank Analysis; FAS; SAP V3.0)

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)	

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.
[Source: Sponsor]

As the table indicates, when analyzed according to Version 3 of the SAP, the primary efficacy analysis of Study 301 failed to reach statistical significance (p=0.07).

During the trial, 4 subjects dropped out because of an adverse event (AE) without receiving rescue medications. According to Version 3 of the SAP, these subjects were all conservatively ranked in the group that received rescue therapy. However, 3 of these 4 subjects actually met the protocol-defined criteria for disease improvement at the time of drop out. Dr. Breder's review provides a detailed discussion of these cases, including the individual clinical narratives provided by the applicant. I agree with both Dr. Breder and Dr. Qui that Version 3 of the SAP treats these subjects too conservatively based upon their actual clinical progress during the trial. Version 2 of the SAP would have used an LOCF approach for MG-ADL scores to rank these 3 subjects. As noted, the Division had not objected to Version 2 of the SAP, which clearly seems to be a more appropriate analysis for the trial's primary endpoint. The following table, copied from Dr. Qui's review, presents the results of the primary efficacy analysis based on Version 2 of the SAP.

Table 3-7 Change from Baseline in Myasthenia Gravis Activities of Daily Living Total Score at Week 26: (ANCOVA Worst –Rank Analysis; FAS; SAP V2.0)

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)	70.2(4.41)	54.8(4.46)	-15.4	0.0160
	95% CI for LS Mean	(61.41, 78.89)	(45.97, 63.63)	(-27.80, -2.92)	
Note: p-value from worst rank ANCOVA model to test whether treatment groups 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 with worst ranks based on time to death, time to MG crisis, time to Drop-out due to ADL Worsening, time to rescue therapy, and finally change in MG-ADL at Week 26 or LOCF with greatest improvement getting the rank of 1					

[Source: Sponsor]

As the table indicates, when analyzed according to Version 2 of the SAP, the primary efficacy analysis of Study 301 was statistically significant (p=0.02).

The worst-rank analysis does not allow for an estimate of the treatment effect size on the MG-ADL scale as the analysis is based on overall subject ranks, and not scale performance. Dr. Qui's review presents the results of a sensitivity analysis using an ANCOVA analysis with LOCF for the change from baseline to Week 26 in MG-ADL scores, as described in the following applicant table copied from her review:

Table 3-15 Change from Baseline in MG-ADL Total Score at Week 26: (ANCOVA; FAS)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Change from Baseline (1)	LS Mean (SEM)	-2.6 (0.48)	-4.0 (0.48)	-1.4	0.0390
	95% CI for LS Mean	(-3.52, -1.63)	(-4.96, -3.04)	(-2.77, -0.07)	
Baseline MG-ADL Total Score	n	63	62		
	Mean (SD)	9.9 (2.58)	10.5 (3.06)		
	Median	9.0	10.0		
	Min, Max	5, 18	5, 18		
Week 26 MG-ADL Total Score (LOCF)	n	63	62		
	Mean (SD)	7.4 (3.50)	6.4 (4.76)		
	Median	7.0	6.0		
	Min, Max	0, 16	0, 17		
Change from Baseline to Week 26 in MG-ADL Total Score	n	63	62		
	Mean (SD)	-2.4 (3.32)	-4.1 (4.48)		
	Median	-2.0	-4.0		
	Min, Max	-8, 7	-15, 4		

(1) LS Means are from the ANCOVA model.
Note: p-value from ANCOVA analysis of change from baseline, testing for the effect of treatment, with the baseline value and the pooled MGFA randomization stratification variable as covariates in the model. For patients who did not require rescue therapy, if the Week 26 MG-ADL total score was missing or an item from the Week 26 MG-ADL was missing, last observation carried forward (LOCF) was used for missing Week 26 MG-ADL total score or missing item was missing or an item from the Week 26 MG-ADL was missing, last observation carried forward (LOCF) was used for missing Week 26 MG-ADL total score or missing item of the Week 26 MG-ADL. For patients requiring rescue therapy, the last observation prior to the first use of rescue therapy was used. If the last observation prior to the first use of rescue therapy was missing an item from the MG-ADL, last observation carried forward was used for the missing item.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Max = maximum; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGFA = Myasthenia Gravis Foundation of America; Min = minimum; SD = standard deviation; SEM = standard error of the mean.

This table depicts a 1.4-point greater improvement from baseline at Week 26 in MG-ADL scores in eculizumab-treated subjects compared to placebo-treated subjects (nominal p=0.04).

The protocol prespecified the following secondary endpoints that were analyzed using a hierarchical testing procedure to control for Type I error (i.e., if the analysis of any endpoint failed to reach statistical significance, the analysis of any lower-ranked endpoints could then not be considered to be statistically significant).

- Change from baseline to Week 26 in Quantitative Myasthenia Gravis (QMG) scores
- Proportion of subjects with at least a 3-point reduction in MG-ADL total scores from baseline to Week 26 (without rescue therapy)
- Proportion of subjects with at least a 5-point reduction in QMG total scores from baseline to Week 26 (without rescue therapy)
- Change from baseline to Week 26 in the Myasthenia Gravis Composite (MGC) score
- Change from baseline to Week 26 in the Myasthenia Gravis – Quality of Life 15 (MG-QoL15) score

Descriptions of the QMG, MGC, and MG-QoL15 scales are provided in Dr. Breder's review.

The following table, generated based on Dr. Qui's review, provides a high-level summary of the results of the secondary endpoint analyses from Version 3 the SAP. The reader is referred to Dr. Qui's review for additional details.

Secondary Endpoint Analyses (SAP VERSION 3)					
Endpoint	**Statistic**	**Placebo (N=63)**	**Eculizumab (N=62)**	**Treatment Difference**	**p-value**
QMG (worst-rank; change from baseline to Week 26)	Ranked Score LS Mean (SEM)	70.7 (4.46)	54.7 (4.50)	-16.0	0.01
Proportion with 3-point reduction in MG-ADL Total Score from baseline to Week 26 (no rescue therapy)	n/N (%)	25/63 (39.7)	37/62 (59.7)	20.0	0.02
Proportion with 5-point reduction in QMG Total Score from baseline to Week 26 (no rescue therapy)	n/N (%)	12/63 (19.0)	28/62 (45.2)	26.2	0.002
MGC (worst-rank; change from baseline to Week 26)	Ranked Score LS Mean (SEM)	67.7 (4.47)	57.3 (4.52)	-10.5	0.10
MG-QoL15 (worst-rank; change from baseline to Week 26)	Ranked Score LS Mean (SEM)	69.7 (4.51)	55.5 (4.55)	-14.3	0.03

The analyses of the two responder-based secondary endpoints do not rely on worst-rank analyses and are therefore the same between Version 2 and 3 of the SAP. However, it is very reasonable to consider the results of the additional endpoint analyses, which are based on worst-rank analyses, using Version 2 of the SAP for the same reasons that this was a more appropriate approach to the analysis of the primary efficacy endpoint. The following table summarizes the p-values for the worst-rank analyses of the QMG, MGC, and MG-QoL15 based on Version 2 of the SAP.

Secondary Endpoint Analyses – Worst Rank Analyses Only (SAP VERSION 2)	
Endpoint	**p-value**
QMG (worst-rank; change from baseline to Week 26)	0.01
MGC (worst-rank; change from baseline to Week 26)	0.04
MG-QoL15 (worst-rank; change from baseline to Week 26)	0.001

An important difference between using Versions 2 and 3 of the SAP for the analyses of the secondary endpoints is that the analysis of the 4th endpoint, the MGC, is statistically significant based on Version 2. The statistical significance of this endpoint then preserves alpha for the analysis of the MG-QoL15, which is also statistically significant. Using this approach, all of the 5 hierarchically-ordered secondary endpoints are statistically significant in favor of eculizumab.

Dr. Qui's review also includes the following two figures, which present descriptive responder analyses for both the MG-ADL and QMG scales, respectively.

Figure 1 MG-ADL Responder Analysis without Rescue at Week 26

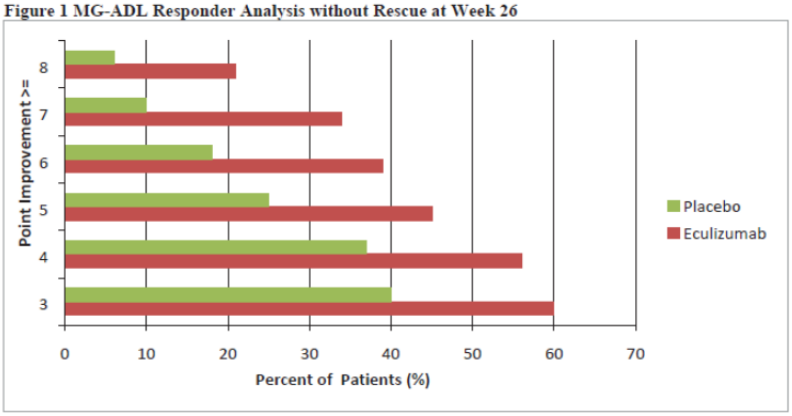
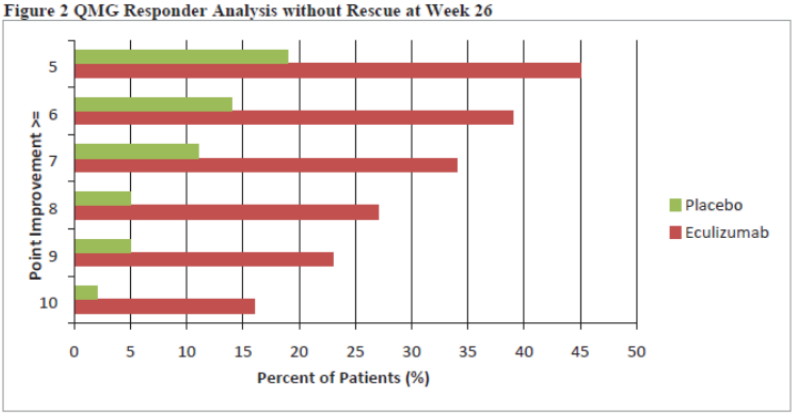


Figure 2 QMG Responder Analysis without Rescue at Week 26



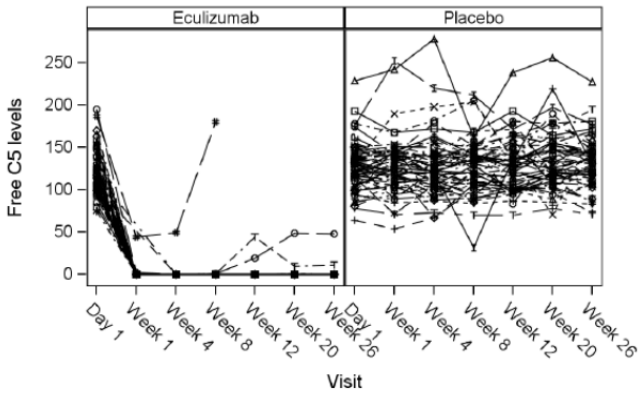
As Dr. Qui notes, at increasing levels of response for both scales, the proportion of responders consistently favors eculizumab.

Dr. Qui's review discusses a number of sensitivity analyses, which all support the results of the efficacy analyses presented above.

A consideration in the review of Study 301 relates to the fact that following database lock on April 15, 2016, the applicant states that it noted some inconsistent data entries for key parameters. As a result, the applicant reported that the database was unlocked on April 22, 2016, to verify the clinical deterioration and rescue medication data for all subjects. The database was again locked on June 1, 2016, with the applicant indicating that specific records in the clinical database were unlocked for a total of 7 subjects. A detailed discussion of this history is included in Dr. Breder's review. As Dr. Breder notes, this issue was a target of the Office of Scientific Investigation (OSI) inspect of the applicant during the review. The OSI review concludes that, based on the results of these inspections, the data submitted by the applicant are acceptable. This inspection did not find that any changes to other subject's data were made following the initial database lock based on a random sampling of audit trails.

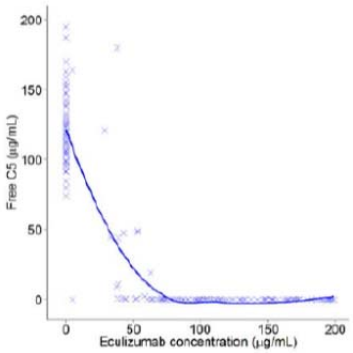
The OCP review presents an analysis of reductions in free complement protein C5 levels in Study 301 as a supportive exploratory PD marker of efficacy, as depicted in the following figure copied from that review. As eculizumab is designed to bind to the C5 protein, you would expect to see reductions in C5 levels with treatment.

Figure 4. Free C5 Levels in Eculizumab and Placebo Groups at Various Visits in Study ECU-MG-301



These results are further supported by an evaluation of free C5 concentrations graphed versus eculizumab concentrations from Study 301, as depicted in the following applicant figure, copied from the OCP review.

Figure 5. Scatter Plot of Free C5 Concentration Vs Eculizumab Concentration in Study ECU-MG-301



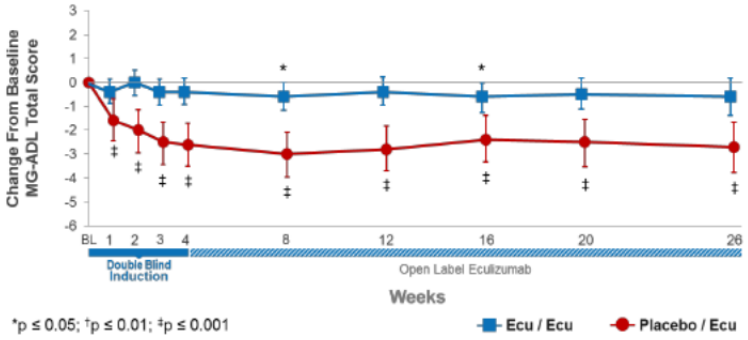
Source : Figure 14 on Page 73 in ecu-mg-adult-pk-pd-study-report.pdf

Study ECU-MG-302 (Study 302)

Following completion of Study 301, subjects were eligible to enroll in Study 302, which was an open-label extension trial. The primary objective of the trial was to evaluate the long-term safety of eculizumab in subjects with gMG, although data on the efficacy endpoints were also collected. Upon enrollment, subjects first entered a blinded 4-week Induction phase. This period was designed to initiate treatment in subjects who received placebo during Study 301 while maintaining the blinding to subjects' original treatment assignments in Study 301. Subjects who had been randomized to the placebo arm in Study 301 would receive 900mg IV eculizumab week through Week 4, while subjects who were randomized to eculizumab in Study 301 would receive 1200 mg IV eculizumab at Weeks 1 and 3 and placebo on Weeks 2 and 4. All subjects would then receive 1200 mg IV eculizumab every other week starting at Week 5. Despite this blinding to the original treatment assignment, subjects and investigators were aware of the 26-week duration of Study 301, so they would presumably know that all subjects were receiving active treatment. A total of 114 subjects received at least 1 dose of study drug in Study 302.

Dr. Breder's review notes that the application refers to the change from baseline in MG-ADL scores as primary efficacy endpoint, to be analyzed using a repeated-measures model. However, the SAP for Study 302 describes summarizing these results at each visit and does not provide a statistical model, significance level, or approach to Type I error control for this analysis. Therefore, these results are exploratory only and statistically significance can only be considered as nominal. The following figure from the application, copied from Dr. Breder's review, summarizes the change from baseline in MG-ADL scores from Study 302 (again, the applicant's p-values are nominal).

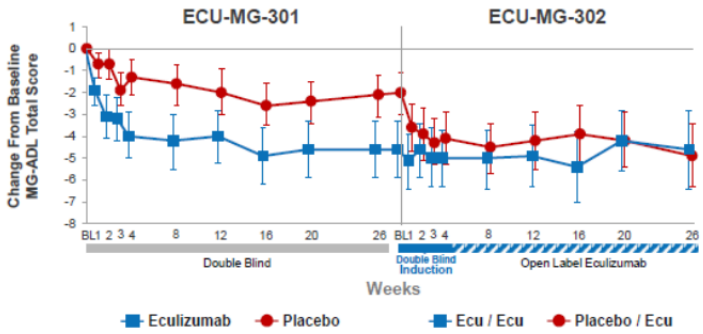
Figure 3: Change from Baseline in MG-ADL Total Score (LS Mean and 95% CI) by Treatment Arm over Time from ECU-MG-302 Baseline to Week 26 in Study ECU-MG-302 Using a Repeated-Measures Model – Extension Full Analysis Set



Note: The LS mean and 95% CI are based on a Repeated-Measures model of change from ECU-MG-302 Baseline in MG-ADL total score for the treatment arms of placebo/eculizumab and eculizumab/eculizumab separately. Each Repeated-Measures model included the following terms: visit and MG-ADL total score at Baseline. Missing values were not imputed. Nominal p-values are for the statistical significance testing of the mean change from ECU-MG-302 Baseline in MG-ADL total score by visit using a Repeated-Measures model for each arm.
Abbreviations: BL = Baseline; CI = confidence interval; Ecu = eculizumab; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living profile
Source: Table 14.2.1.5.1, Table 14.2.1.6.1, Figure 14.2.1.1.1.3

The following figure from the application, copied from Dr. Breder's review, presents the change from baseline in MG-ADL Total Score for both Study 301 and Study 302.

Figure 4: Change from Baseline in MG-ADL 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



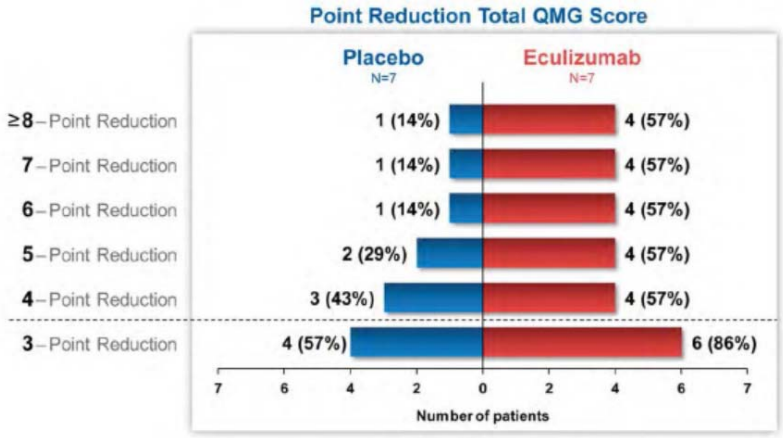
Note: 95% CI is based on t-distribution for each treatment arm at each visit.
Abbreviations: BL = Baseline; CI = confidence interval; Ecu = eculizumab; MG-ADL = Myasthenia Gravis Activities of Daily Living profile
Source: Table 14.2.1.3.1, Figure 14.2.1.1.1.1

Although only a descriptive analysis, this figure depicts a discernable change in the trajectory of the course in subjects who were initially treated with placebo in Study 301 during the blinded transition phase of Study 302. A very similar pattern of results was also present for the exploratory analyses of the QMG and MGC endpoints, as described in Dr. Breder's review.

Study C08-001

This was an early-phase, randomized, double-blind, cross-over trial in subjects with refractory gMG. Period 1 involved 16 weeks of treatment on eculizumab or placebo. Following a 35-day wash-out period, subjects then received the alternative treatment from Period 1 in Period 2. A total of 14 subjects were enrolled in Study C08-001 and randomized in a 1:1 ratio to treatment or placebo. The dosing in this trial was lower than in Study 301, with subjects receiving 600 mg IV (or matching placebo) weekly for 4 weeks, followed by 900 mg IV (or matching placebo) one week later and then every 2 weeks thereafter. Additional details of this trial design are included in Dr. Breder's review.

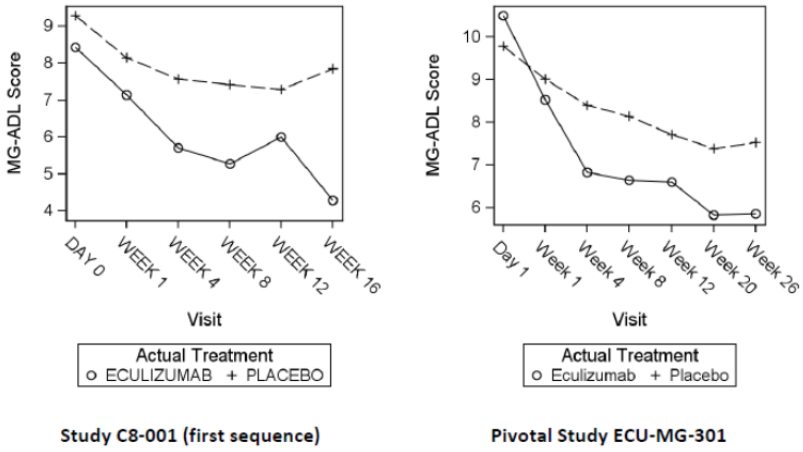
The primary efficacy analysis was intended to be the difference between treatment arms in the percentage of subjects with a 3-point reduction from baseline in the QMG total score at the end of each treatment period. A number of secondary endpoints were also evaluated, without control for Type I error. Dr. Breder's review notes that there was a carryover effect in Period 2, so only the results from Period 1 can be considered. The analysis of Period 1 only was not prespecified and therefore can only be considered descriptively. The following figure, copied from Dr. Breder's review, depicts the proportion of subjects by treatment arm for various degrees of change in QMG score in Period 1.



Nominal p-values have not been provided for this analysis. Descriptively, these results favor eculizumab. Dr. Breder's review also describes the exploratory results of the trial's additional endpoints which also generally favor eculizumab.

The OCP review also compared the changes in MG-ADL score by week between Study C8-001 and Study 301, as depicted in the following figure copied from that review:

Figure 3. Changes in MG-ADL Score by Week in Study C8-001 and ECU-MG-301.



Study C8-001 (first sequence) **Pivotal Study ECU-MG-301**

The OCP review notes that similar trends in MG-ADL improvement can be observed in both trials, although there was more of a placebo response in Study 301. The OCP review concludes that this trend in MG-ADL response in Period 1 of Study C8-001 can be considered to be supportive evidence of efficacy.

Efficacy Conclusions

The 1998 FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products describes scenarios where evidence from a single clinical study can fulfil the criteria for providing substantial evidence for effectiveness under 21 CFR 314.126. The Guidance also refers to section 115(a) of the FDA Modernization Act (1988) which states that the Agency may also consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence of effectiveness in support of an approval of a marketing application.

The primary efficacy analysis of Study 301 failed to reach statistical significance when analyzed according to Version 3 of the SAP (p=0.07), which was the version in place at the time of data analysis. This result was based on a worst-rank analysis which ranked subjects with respect to MG-ADL scores, the need for rescue medication, MG crisis, discontinuation, and death. Importantly, Version 3 of the SAP conservatively grouped all subjects who discontinued for any reason but who did not receive rescue therapy as equivalent to those subjects who received rescue therapy. Version 2, however, would only assign these subjects to the rescue therapy group if they met the protocol-defined criteria for clinical worsening based on MG-ADL score changes. If they did not meet these criteria, their MG-ADL scores would be ranked based on a LOCF approach. The Division had not objected to this approach when it had previously reviewed Version 2 of the SAP.

Four subjects discontinued from the trial but did not receive rescue medication. However, 3 of these subjects on eculizumab discontinued because of AEs, but actually met the protocol-defined criteria for clinical improvement at the time of discontinuation. Therefore, treating these subjects conservatively, as per Version 3 of the SAP, does not fully capture their treatment response. When the data are analyzed according to Version 2 of the SAP, the results of the primary efficacy analysis become statistically significant (p=0.02). It is not common that the failure of a prespecified primary efficacy analysis can be mitigated. However, in my opinion, Version 2 of the SAP is clearly a more informative approach to the analysis of Study 301 and should be utilized.

The protocol also analyzed 5 secondary endpoints that were hierarchically ordered to control for Type I error. The endpoints included worst-rank analyses of QMG, MGC, and MG-QoL15 scores, as well as responder-based analyses of the MG-ADL and QMG. When analyzed using Version 3 of the SAP, 3 of these 5 endpoints reached statistical significance and 1 more reached nominal significance. However, when using Version 2 of the SAP, which is clearly more appropriate here for the same reasons that it was more appropriate for the primary efficacy analysis, all 5 endpoints reach statistical significance.

Ultimately, when using the most appropriate version of the SAP for the analysis of Study 301, the primary efficacy analysis and the analyses of all 5 pre-specified secondary efficacy analyses are statistically significant. These results are robust and support the ability of Study 301 to be considered a single adequate and well-controlled trial that establishes the effectiveness of eculizumab for the treatment of gMG. Additionally, the fact that these effects were observed in a treatment-refractory population further adds to the strength of the trial's results.

In my opinion, the results from Study 301 alone support the effectiveness of eculizumab for the treatment of gMG without the need for confirmatory evidence. I do agree with Dr. Breder that the results of Study 302 and Study CN08-001 (Period 1) provide some additional supportive evidence of effectiveness, albeit not required in this circumstance. The efficacy results from these trials can only be considered descriptively. However, the pattern of results in both trials is reassuringly highly consistent with the findings with Study 301 across a number of different endpoints.

A final consideration relates to the proposed indication statement. The applicant has proposed that indication (b) (4) As will be discussed in Section 7 of this review, when patients are appropriately vaccinated, the risk of such infections appears to be low. Therefore, my recommendation is that eculizumab should be indicated for all patients with gMG who are anti-AchR antibody positive. Healthcare providers and patients can then make informed decisions about the use of eculizumab based on clinical judgment and patient preference.

7. Safety

Dr. Breder's review notes that 133 unique subjects were exposed to eculizumab in the gMG development program. Of these, 50 have been exposed to eculizumab for 52 weeks in Studies 301 and 302. As eculizumab is FDA-approved for the treatment of PNH and aHUS, the main focus of Dr. Breder's safety review was to confirm that there were no unexpected safety findings in the gMG population that are not already known and described in the current prescribing information (PI) for Soliris. Dr. Breder also analyzed the common AEs from Study 301 for inclusion into Section 6 of the PI. I agree with Dr. Breder that the safety database is adequate in the context of a drug that is FDA-approved for indications that have similar risk/benefit considerations to gMG.

The following are among the key conclusions of Dr. Breder's review of safety information contained in the application:

- One subject in the eculizumab arm in Study 301 died due to complications of an MG crisis after discontinuing on study Day 128. One other subject died during Study 302 as a result of cytomegalovirus (CMV) hepatitis, multi-organ failure, and sepsis. Neither of these events were likely related to treatment with eculizumab.

- In Study 301, 18/63 (29%) subjects in the placebo arm reported at least one serious adverse event (SAE) as compared to 9/62 (15%) in the eculizumab arm. In total, 33 SAEs were reported in the placebo arm as compared to 17 in the eculizumab arm. The system organ class (SOC) of Infestations and Infections was the most frequently reported SAE, experienced by 6/63 (10%) of subjects in the placebo arm as compared to 3/62 (5%) of subjects in the eculizumab arm.

- There were only 7 discontinuations from Study 301, including 5 from the eculizumab arm and 2 from the placebo arm. Of the 5 discontinuations in the eculizumab arm, 4 were related to adverse events (bacteremia, intestinal perforation, MG crisis, and metastatic prostate cancer) and 1 was due to a withdrawal of consent related to a "failure of benefit." The 2 subjects in the placebo arm who discontinued did so due to withdrawal of consent with limited additional details provided. A review of the narratives for these events suggests that they are not likely to be related to treatment with eculizumab.

- Dr. Breder notes that his review of the Medical Dictionary for Regulatory Activities (MedDRA) coding of the verbatim terms to preferred terms (PTs) for the AEs in Study 301 and Study 302 resulted in his recoding approximately 33 unique terms, mainly for the purposes of consolidation of similar events (e.g., abdominal pain upper, abdominal pain lower, and gastrointestinal pain were all re-coded to abdominal pain).

- The following table, reproduced based on Dr. Breder's review, summarizes the AEs with an incidence on treatment of greater than 5% and that occurred more frequently than in placebo (note that this table rounded to the nearest whole number which resulted in 3 events no longer demonstrating a greater incidence than placebo as compared to Dr. Breder's review).

PT	SOC	Eculizumab N=62 n(%)	Placebo N=63 n(%)
Musculoskeletal pain	Musculoskeletal and connective tissue disorders	9 (15)	5(8)
Abdominal pain	Gastrointestinal disorders	5(8)	3(5)
Contusion	Injury, poisoning and procedural complications	5(8)	2(3)
Herpes-related infection	Infections and infestations	5(8)	1(2)
Edema peripheral	General disorders and administration site conditions	5(8)	3(5)
Pyrexia	General disorders and administration site conditions	4(7)	2(3)

- No abnormal signals of concern were observed in the analyses of the laboratory data or investigations (e.g., electrocardiograms) from the trials.

- The current PI for eculizumab has a black box warning and a risk evaluation and mitigation strategy (REMS) for serious meningococcal infections. All subjects in the development program for eculizumab were vaccinated against *Neisseria meningitides* at least 14 days prior to treatment, if not already previously vaccinated within the time period of active coverage specified by the vaccine manufacturer. Dr. Breder concludes that there were no such apparent cases of infection observed in the gMG clinical trials.

- Dr. Breder also concludes that there do not appear to be any safety signals (or loss of efficacy) that could be related to immunogenicity. No subjects in the eculizumab arm tested positive for ADA after treatment with eculizumab had been initiated (although the assays cannot exclude the presence of low-levels of ADA as discussed in Section 2 of this memo).

I agree with Dr. Breder's conclusion that no new safety signals for eculizumab have been identified in the current application that have not previously been identified and described in product labeling.

8. Advisory Committee Meeting

Not applicable.

9. Pediatrics

Only in very rare cases is gMG diagnosed in children and adolescents. In addition, this development program has orphan designation, so the submission of a Pediatric Study Plan (PSP) is not required.

10. Other Relevant Regulatory Issues

- No Good Clinical Practice (GCP) issues were identified during the review of this application.

- Dr. Breder concludes that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

- The Office of Scientific Investigations (OSI) has investigated four clinical investigator sites (three foreign, one domestic) and the applicant. As already discussed, the applicant inspection was related primarily to the issue of the database being unlocked for Study 301. The OSI review concludes that based on the results of these inspections, the data submitted by the applicant from these sites are acceptable, and the trials were adequately conducted.

- Soliris has a REMS for the PNH and aHUS indications that was originally approved on June 4, 2010, to mitigate the risk of meningococcal infection and hemolysis post-discontinuation. The Division of Risk Management (DRISK) review states that the REMS has been modified six times and consists of a Medication Guide, elements to assure safe use, and a timetable for submission

of assessments. The applicant has submitted a REMS modification as part of this supplemental BLA. The only change to the REMS will be to include the new gMG indication.

DRISK requests an assessment of prescriber and patient understanding regarding the safe use of eculizumab for the treatment of gMG. Additionally, DRISK finds the prescriber and patient surveys should be reinstated for the PNH and aHUS indications; this in part is due to recent changes to an Advisory Committee on Immunization Practices' meningococcal immunization recommendations, as well as other concerns related to the most recent REMS assessment report that was submitted as part of the efficacy supplement. DRISK also requests that the applicant provide additional details that describe the process of identifying and correcting non-compliance in the prescribing population, which is expected to increase in number.

11. Labeling

Please refer to the final negotiated product label. The following are among the key labeling issues that have been considered during this review:

- The proposed indication statement refers to the (b) (4). However, there is no reason (b) (4) this indication (b) (4) .
- The CLINICAL STUDIES section of the labeling should only include statistically valid and non-redundant results from Study 301 and will be revised accordingly.
- The AE data from the gMG program will be added to the ADVERSE REACTIONS section of the label.
- The applicant has also proposed a number of changes to other sections of the label which have been reviewed both by the DNP review staff as well as the Division of Hematology Products (DHP), as appropriate.

12. Postmarketing Recommendations

There are no postmarketing recommendations for this application.

13. Recommended Comments to the Applicant

There are no additional recommended comments for the applicant.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICHOLAS A KOZAUER
10/23/2017

ERIC P BASTINGS
10/23/2017
I concur, and will issue an approval letter for this sBLA.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166Orig1s422

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Biological License Application (BLA)
Application Number(s)	125166 Supplement 422 (Sequence 572)
Priority or Standard	Standard
Submit Date(s)	12/23/16
Received Date(s)	12/23/16
PDUFA Goal Date	10/22/2017
Division/Office	Division of Neurology Products
Reviewer Name(s)	Christopher Breder, MD PhD
Review Completion Date	10/1/17
Established Name	eculizumab
(Proposed) Trade Name	Soliris
applicant	Alexion Pharmaceuticals, Inc.
Formulation(s)	Injection, Solution
Dosing Regimen	Initiate with 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later and then every 2 weeks thereafter.
applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (anti-AChR) antibody positive.

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1 Executive Summary

1.1. Product Introduction

- Non-proprietary name / Proprietary name - eculizumab / Soliris®
- The pharmacologic class - Humanized monoclonal antibody; Immunosuppresant; proposed mechanism – binds to and inhibits effect of the complement protein C5
- Dosing regimen(s), route of administration, dosage form
- The proposed indication - [redacted] (b) (4)
- Previous approvals:
  - Treatment of paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
  - The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy

1.2. Conclusions on the Substantial Evidence of Effectiveness

Since the eculizumab myasthenia gravis program consisted of only one study that prospectively defined its primary endpoint, my task was to determine if that study stood on its own to provide substantial evidence or if not, whether confirmatory evidence from other sources of data, such as the 302 study or the first period of CN8-0100 could serve as confirmatory evidence. While 'confirmatory evidence' is largely undefined in regulatory statutes and guidances, it generally constitutes some evidence other than that resulting from an effect on a clinically meaningful outcome measured in an adequate and well-controlled study (USFDA 2017).

I believe that the applicant has satisfied this requirement with a positive primary endpoint, the change in the total score for the Myasthenia Gravis Activities of Daily Living scale (MG-ADL Total Score) in the main study, '301' (P=0.0390). The finding is supported in the 301 study by positive results from several secondary measures where an analysis plan used hierarchical analysis to protect the alpha testing level of 0.05. A full description of these results is found in Section 7.1.2. As I discuss in the integrated review of effectiveness, I believe the evidence provided in this study provides sufficient data to satisfy the 'single trial' basis for approval.

Supportive (i.e., not needed for approval based on 301 alone) evidence also comes from a particularly persuasive effect demonstrated in the 301-extension study, 302, where, in the time period with the treatment was still blinded, the subjects on placebo demonstrated a nominally positive treatment effect on amongst other endpoints, the MG ADL and QMG scales. The effect of patients on eculizumab in the 301 study was maintained through the extension study. I also believe the first period of the crossover study, CN08-001 contained supportive evidence. In this small study, patients in the first period before crossover demonstrated a nominally positive effect on the QMG and MGADL scales.

2 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Myasthenia Gravis (MG) is a debilitating, autoimmune neurologic disorder caused by the failure of neuromuscular transmission due to binding of autoantibodies at the neuromuscular junction). Most commonly these autoantibodies are specific for acetylcholine receptors, which are essential for the transmission of nerve impulses to muscle by the neurotransmitter acetylcholine. The disease is characterized by a high mortality rate (about 30% within the first 7 years of diagnosis) and periodic exacerbations through the clinical course of the disease (Oosterhuis 1989). At present, only Pyridostigmine, an acetylcholinesterase inhibitor is approved for the treatment of MG (USFDA 2001). This drug has limitations because its effect is only symptomatic. Nicotinic and muscarinic adverse effects limit its tolerability; overdosing PYR can lead to further muscle weakness (Evoli, Iorio et al. 2016). Edrophonium chloride (Tensilon®, ICN) mentions MG in its labeling but only as a diagnostic aid.

Eculizumab is a recombinant monoclonal antibody that specifically binds to complement protein C5, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. The role of uncontrolled terminal complement activation in the destructive disease processes at the NMJ due to AChR auto-antibody binding at the motor endplate is well accepted by the scientific and clinical community focused on this disease. Inhibition of terminal complement activation is therefore a biologically rational approach to prevent the tissue damage and impaired neuromuscular transmission in patients with MG. Eculizumab is approved in various countries including the United States, the European Union, and Japan for the treatment of Paroxysmal Nocturnal Hemoglobinuria and atypical Hemolytic Uremic Syndrome.

The application contains data from one adequate and well controlled trial ('301'), its extension study, which was open-label but where the treatment in 301 remained blinded, and a small crossover study , CN08-001, where data from the first period was evaluated to support the '301' trial. The primary endpoint for 301, the change from baseline to endpoint of the Myasthenia Gravis Activities of Daily Living total score, from which the substantial evidence is derived, was statistically positive ($P = 0.0390$) and is supported by secondary endpoints from this trial tested using a hierarchy to preserve alpha, as well as nominally positive findings from the 302 and CN08-001 studies.

No new safety findings were apparent from my review of this application. Eculizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risk of meningococcal infections. There is no recommendation to modify the REMS based on the MG development program.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Myasthenia Gravis (MG) is a debilitating, acquired autoimmune neurologic disorder caused by the failure of neuromuscular transmission due to binding of autoantibodies at the neuromuscular junction (NMJ). Most commonly these autoantibodies are specific for acetylcholine receptors (AChRs), which are essential for the transmission of nerve impulses to muscle by the neurotransmitter acetylcholine. The disease is characterized by a high mortality rate (about 30% within the first 7 years of diagnosis) and periodic exacerbations through the clinical course of the disease (Oosterhuis 1989).	Myasthenia Gravis is a serious disease. Although a small population will experience remission, the typical clinical course involves either a protracted course of relapses (50%) with death coming in 7 years for ~30%.
Current Treatment Options	At present, only Pyridostigmine, an acetylcholinesterase inhibitor (AchEi) approved in 1955, has an indication for the treatment of MG (USFDA 2001). This drug has limitations because its effect is only symptomatic. Nicotinic and muscarinic adverse effects limit its tolerability; overdosing PYR can lead to further muscle weakness (Evoli, Iorio et al. 2016). Edrophonium chloride (Tensilon®, ICN) mentions MG in its labeling but only as a diagnostic aid.	There is a high unmet medical need for treatments of Myasthenia Gravis.
Benefit	Eculizumab is a recombinant monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. The role of uncontrolled terminal complement activation in the destructive disease processes at the NMJ due to AChR auto-antibody binding at the motor endplate is well accepted by the scientific and clinical community focused on this disease. Inhibition of terminal complement activation is therefore a biologically rational approach to prevent the tissue damage and impaired neuromuscular transmission in patients with MG. The application contains data from one adequate and well controlled trial ('301'), it's extension study that was open label, but where the treatment in 301 remained blinded, and a small crossover study, CN08-001, where data from the first period was evaluated to support the 301 trial. The primary endpoint for 301, the change from baseline to endpoint of the Myasthenia Gravis Activities	The applicant has established that eculizumab is effective as a treatment for generalized Myasthenia Gravis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of Daily Living total score from which the substantial evidence is derived was statistically positive (P = 0.0390) and is supported by secondary endpoints from this trial which were tested using a hierarchy to preserve alpha, as well as findings from the 302 and CN08-001 studies. The primary endpoint, the MGADL, measures the functional status of myasthenic patients and which is considered clinically meaningful. This is consistently supported by the secondary endpoint, the Quantitative Myasthenia Gravis test is a strength assessment that supports the findings of the MGADL (Barohn, McIntire et al. 1998). Similarly, the Myasthenia Gravis Quality of Life 15-item scale (Burns, Grouse et al. 2010) was statistically positive when using the hierarchical testing of secondary endpoints, which supports the primary, as well. The 301 trial stands on its own to support the approval of eculizumab for this indication. Nominally positive evidence from 302 and CN08-001 support this but are not necessary for approval.	
Risk	Eculizumab is approved in various countries including the United States, the European Union, and Japan for the treatment of Paroxysmal Nocturnal Hemoglobinuria and atypical Hemolytic Uremic Syndrome. The US Package insert carries Warnings and precautions for infections including serious meningococcal infections and infusion reactions. The data from the current application do not mitigate these Warnings so no changes are proposed. There were no new safety signals detected in the program.	The risks of eculizumab treatment are consistent with the current labeling. The serious nature of Myasthenia Gravis justifies an approval action in the setting of the established efficacy of eculizumab.
Risk Management	• Eculizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risk of meningococcal infections. There is no recommendation to modify the REMS based on the MG development program.	No findings from this application mitigate the risks described in the Soliris REMS and so no modifications to the REMS are recommended.

3 Therapeutic Context

3.1. Analysis of Condition

Myasthenia Gravis (MG) is a debilitating, acquired autoimmune neurologic disorder caused by the failure of neuromuscular transmission due to binding of autoantibodies at the neuromuscular junction (NMJ). Most commonly these autoantibodies are specific for acetylcholine receptors (AChRs), which are essential for the transmission of nerve impulses to muscle by the neurotransmitter acetylcholine. The disease is characterized by a high mortality rate (about 30% within the first 7 years of diagnosis) and periodic exacerbations through the clinical course of the disease (Oosterhuis 1989). Although a small population will experience remission, the typical clinical course involves either a protracted course of relapses (50%) with death coming in 7 years for ~30%.

3.2. Analysis of Current Treatment Options

At present, only Pyridostigmine, an acetylcholinesterase inhibitor (AchEi) has been approved for the treatment of MG since 1955 (USFDA 2001). This drug has limitations because its effect is only symptomatic. Nicotinic and muscarinic adverse effects limit its tolerability; overdosing PYR can lead to further muscle weakness (Evoli, Iorio et al. 2016). Edrophonium chloride (Tensilon®, ICN) mentions MG in its labeling but only as a diagnostic aid.

4 Regulatory Background

4.1. U.S. Regulatory Actions and Marketing History

Soliris® was originally given accelerated approval on March 16, 2007, for the treatment of paroxysmal nocturnal hematuria (PNH). At the time of approval, the product labeling contained a Boxed Warning for meningococcal infection and a Medication Guide. A Risk Evaluation and Mitigation Strategy (REMS) was imposed that includes the Medication Guide, Elements to Assure Safe Use (ETASU), and a timetable for assessments.

On April 30, 2013, Soliris was approved for hemolytic uremic syndrome (aHUS). This supplement provided supporting data to convert the accelerated approval to regular approval for the treatment of patients with atypical Hemolytic Uremic Syndrome (aHUS).

As of the Annual report for 2017 (rec'd 05 May 2017), (b) (4) have been distributed domestically.

4.2. Summary of Presubmission/Submission Regulatory Activity

- Pre-IND meeting scheduled for March 4, 2008 – FDA Preliminary Responses
    - Discussions regarding primary endpoint, risk/benefit of expected AE of infections, replication, trial duration, safety database
- Type B, End-of-Phase 2 (EOP2) meeting on March 20, 2013
    - Discussions regarding single Ph3 trial, need for functional co-primary endpoint, safety database, patient selection, immunogenicity
- Type C (face-to-face) meeting on September 14, 2016 to discuss pre-specified primary and secondary endpoint analyses from study ECU-MG-301
    - Discussions on adequacy of studies supporting supplement, indication
    - sponsor presented slides of data intended to support application
- Type B, Pre-sBLA meeting scheduled for December 14, 2016 – FDA Preliminary Comments, dated December 9, 2016

4.3. Foreign Regulatory Actions and Marketing

The foreign regulatory history as of the last AR (05 May 2017) is presented in Table 1 (aHUS) and Table 2 (PNH) (Alexion 2017).

Table 1 Foreign Regulatory History including US for Reference

aHUS				
Country	Dose(s)	Dosage Form(s)	Action[1]	Date
United States	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Accelerated Approval Regular Approval	23 September 2011 30 April 2014
European Union[2]	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	24 November 2011
Algeria	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	23 March 2016
Australia	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	3 October 2012
Brazil	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	13 March 2017
Canada	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval (adults & adolescents aged 13-17 and/or weighing >=40kg); NOC/c for pediatric patients weighing <40kg Full NOC	1 March 2013 30 June 2015
Columbia	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	17 June 2013
Hong Kong	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	29 November 2013
Israel	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	29 December 2011
Japan	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	13 September 2013
Malaysia	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	22 August 2016
Mexico	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	27 August 2015
Russia	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	12 August 2013
South Korea	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	25 August 2015 (ODD License) 18 March 2016 (NDA License)
Switzerland	Adults: 900mg/1200mg ≤ 18 years: 300mg/600mg/900mg	IV dosage form	Approval	25 May 2012

1 Approval, non-approval, withdrawal, or submission
2 Includes 28 countries in the EU plus EEA countries (Norway, Iceland and Lichtenstein)
3 Special Registration: No dossier registered
4 Special Registration: Approved as Service Product

As of the last AR, (b) (4) have been distributed outside of the US.

Table 2 Approval History for the Paroxysmal Nocturnal Hematuria Indication

PNH				
Country	**Dose(s)**	**Dosage Form(s)**	**Action[1]**	**Date**
United States	600mg/900mg	IV dosage form	Approval	16 March 2007
European Union[2]	600mg/900mg	IV dosage form	Approval	20 June 2007
Algeria	600mg/900mg	IV dosage form	Approval	23 March 2016
Australia	600mg/900mg	IV dosage form	Approval	17 February 2009
Brazil	600mg/900mg	IV dosage form	Approval	13 March 2017
Canada	600mg/900mg	IV dosage form	Approval	28 January 2009
Colombia	600mg/900mg	IV dosage form	Approval	10 November 2011
Croatia	600mg/900mg	IV dosage form	Approval	01 July 2013
Hong Kong	600mg/900mg	IV dosage form	Approval	2 April 2012
Iceland	600mg/900mg	IV dosage form	Approval	19 July 2007
Israel	600mg/900mg	IV dosage form	Approval	5 August 2010
Japan	600mg/900mg	IV dosage form	Approval	16 April 2010
Malaysia	600mg/900mg	IV dosage form	Approval	18 April 2012
Mexico	600mg/900mg	IV dosage form	Approval	30 August 2010
New Zealand	600mg/900mg	IV dosage form	Approval	1 September 2011
Norway	600mg/900mg	IV dosage form	Approval	19 July 2007
Russia	600mg/900mg	IV dosage form	Approval	11 November 2011
Singapore	600mg/900mg	IV dosage form	Approval	12 September 2012
Switzerland	600mg/900mg	IV dosage form	Approval	04 January 2010
South Korea	600mg/900mg	IV dosage form	Approval	22 January 2010 (ODD License) 18 Mar 2016 (NDA License)
Taiwan[3]	600mg/900mg	IV dosage form	Approval	4 March 2011
Turkey	600mg/900mg	IV dosage form	Approval	31 July 2014
Venezuela[4]	600mg/900mg	IV dosage form	Approval	8 June 2012

5 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

5.1. Office of Scientific Investigations (OSI)

5.1.1. Site Inspections

Site inspections were based on enrollment numbers and potential effects on the efficacy assessment. DNP collaborated with the OSI (using the site inspection tool) and OB (by performing efficacy analyses by site, particularly considering changes in the imputations described in Section 5.1.2 of this review) team members to determine which sites would be of most value.

Considering the factors described and the location of sites, four were chosen for inspection. No results were found in these inspections that affected the integrity of data submitted in the BLA. A summary by site is provided below.

Site 313 - Stanislav Vohanka, M.D., Czech (2 randomized subjects) Had the subject driving the results after modification of imputation to SAP version 2 (see this review Section X) + no prior inspections. An inspection was conducted at this site between April 18, 2017 and April 21, 2017. The Agency field investigator did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance.

Site 113 - Dr. Casasnova Pons, Spain (5 randomized subjects) This inspection was conducted from 5/22/2017 to 5/26/2017. This site was a high enroller, with one subject that may drive results (though perhaps less than the subject at Site 313); no prior inspections. There were site issues with the timing in reporting of an SAE. The field investigator recommended a classification of No Action Indicated (NAI). A Form FDA 483, Inspectional Observations, was not issued at the close of the inspection. After OSI review of the Establishment Inspection Report (EIR), the inspection was classified as Voluntary Action Indicated (VAI).

Site 167 - Dr. Tuan Vu, USA Florida (6 randomized subjects) This inspection was conducted from May 1, 2017 and May 2, 2017. The site report remarked that it had adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

Site 134- Dr. Jan Bleeker, Belgium (n = 5 randomized) This site was a "high" enroller with the highest number of protocol violations and the second highest number of SAEs [ranked 2 overall in inspection tool]; no prior inspections

5.1.2. **Sponsor inspection**

According to the sponsor's CSR (Section 9.8.1.4.2., p75/208), the database was locked on April 15, 2016. The sponsor noted some inconsistent data entries for key parameters, so the database was unlocked on April 22, 2016 to verify the Clinical Deterioration and rescue medication data for all subjects. The database was relocked on June 1, 2016. The sponsor stated that specific records in the clinical database were unlocked for a total of 7 subjects.

A clinical information request was sent on about 5/19/2017

You have noted in your study report of ECU-MG-301 that the data base was unlocked; we have several questions related to this action:

1. *Did you only unlock the database for these subjects or an entire database containing all subjects?*
2. *What components (variables) of the study did this database contain?*
3. *Did this database have the capacity to provide an audit trail of all changes made at any time? If so please describe the exact type of database and its properties related to audit trails for changes.*
4. *Provide a table for all subjects who had ANY changes in data entries made after the initial database lock, including the subject unique ID, variable changed, data before the change, data after the change, date of change and rationale for change*

The sponsor stated in a response to the CIR that changes were made at the subject level in the

electronic data capture system and that all changes made to the database are captured in the audit trail and available through an audit trail report.

Table 3 Rationale for Changes to the Database Post Database Lock by Patient ID#

Patient #	Rationale
(b) (6)	Clarification on date for clinical deterioration
	Clarification on date for clinical deterioration
	Clarification of criterion for clinical deterioration determination
	Clarification on determination of clinical deterioration
	Clarification on determination of clinical deterioration
	Clarification on date for clinical deterioration
	Clarification on determination of clinical deterioration

The focus of a sponsor inspection was to:

- Verify that no other changes were made to the database other than those described by the sponsor (see background materials)
- Verify that database unlocking followed their SOP (SOP-G-CDM-0001)
- Verify that unlocking of the database did not occur on other occasions
- Verify the audit trail for database changes against those detailed by the sponsor
- Verify the frequency and adequacy of clinical monitoring
- If feasible, review site queries and contact reports and verify with changes made to database
- Review the sponsor's quality control (QC) process (e.g. why were data inconsistencies not noted prior to database lock?)

The final report of this inspection is still pending at the time of this review however a communication from the OSI team stated that the documentation at the sponsor was the same as what they had submitted to us. The audit trails did not show any additional changes to those 7 subjects after the data was relocked. The field investigator also looked at a random sample of other subjects' audit trials and did not see any changes after the initial database lock.

6 Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Table 4 Table of Clinical Studies

Study Type	Study Identifier and Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Patients or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3	ECU-MG-301 M5.3.5.1	Primary Objective: To assess the efficacy of eculizumab as compared with placebo in the treatment of refractory gMG based on the improvement in the MG-ADL Secondary Objectives: 1 Characterize the overall safety and tolerability of eculizumab compared with placebo in refractory gMG patients 2 Assess the efficacy of eculizumab as compared with placebo on: • QMG score • MGC score • Improvement in clinically meaningful primary symptoms 3 Characterize the effect of eculizumab versus placebo on QoL measures 4 Describe the PK and PD of eculizumab in refractory gMG patients.	Randomized, double-blind, parallel-group, placebo-controlled, multicenter study. Patients were stratified at randomization by MGFA class: MGFA Class IIa and IIIa MGFA Class IVa MGFA Class IIb and IIIb MGFA Class IVb	Blinded Induction Phase: eculizumab arm: 3 vials of eculizumab (900 mg IV) at Visits 2 through 5 and 4 vials of eculizumab (1200 mg IV) one week later at Visit 6 Placebo arm: 3 vials of placebo (equivalent to 900 mg IV of IP) at Visits 2 through 5 and 4 vials of placebo (equivalent to 1200 mg IV of IP) one week later at Visit 6 Double-blind Maintenance Phase: Eculizumab arm: 4 vials eculizumab (1200 mg IV) every 2 weeks from Visit 6 to end of study Supplemental doses: 2 vials (600 mg IV) of eculizumab or matching placebo for patients receiving PE for clinical deterioration.	Total: 125 patients eculizumab: n=62; Placebo: n=63	Refractory gMG	2- to 4-week Screening Period, 26-week Study Period, and 8-week Follow-up Period (for patients who withdrew or did not enter the ECU-MG-302 extension study). Overall duration for a patient = up to 38 weeks Per patient: Total exposure to eculizumab: up to 26 weeks Total exposure to placebo; up to 26 weeks	Study completed 19 Feb 2016 (last patient last visit) Full CSR (ECU-MG-301 CSR) Efficacy data are also provided in Module 2.7.3. Safety data are also provided in Module 2.7.4.

Study Type	Study Identifier and Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Patients or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3	ECU-MG-302 M5.3.5.2	Primary Objective: To evaluate the long-term safety of eculizumab in patients with refractory gMG Secondary Objectives: 1 To evaluate long-term efficacy as measured by improvement or maintenance of the MG-ADL 2 To evaluate long-term efficacy by additional efficacy measures: • QMG score • MGC score • improvement or maintenance in primary symptoms 3 To characterize the effect of eculizumab on QOL measures 4 To describe the PK and PD of eculizumab in patients with gMG	Open-label, multi-center, extension of Study ECU-MG-301 A 4-week blind Induction Phase was incorporated into the beginning of the study to preserve the blind in Study ECU-MG-301	Blind Induction Phase: Eculizumab patients from ECU-MG-301: 4 vials of eculizumab (1200 mg IV) every 2 weeks at Visits 1 and 3 and 4 vials of placebo (equivalent to 1200 mg IV of IP) at Visits 2 and 4. Placebo patients from ECU-MG-301: 3 vials of eculizumab (900 mg IV) plus 1 vial of placebo (equivalent to 300 mg IV of IP) weekly at Visits 1 through 4. Open-Label Maintenance Phase: All patients: 4 vials of eculizumab (1200 mg IV) every 2 weeks from Visit 5 to end of study Supplemental doses: 2 vials (600 mg) of eculizumab for patients receiving PE for clinical deterioration.	Total: 113 patients placebo /eculizumab: n=58 eculizumab/ eculizumab: n=55	Refractory gMG	Entry within 2 weeks after completing Visit 17 (Week 26) in Study ECU-MG-301; 4-week blind induction phase; up to 4 years Open-label Maintenance Phase; 8-week Post-treatment Follow-up Phase Per patient: Total exposure to eculizumab: up to 208 weeks	Ongoing Full interim CSR (ECU-MG-302 CSR) Clinical database cut-off date: 01Mar2016 Efficacy data are also provided in Module 2.7.3. Safety data are also provided in Module 2.7.4.

Study Type	Study Identifier and Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Patients or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 2	C08-001 M5.3.5.1	Primary: Safety: TEAEs. Efficacy: Percentage of patients with a 3-point reduction from baseline in QMG total score for disease severity at the end of each treatment period Secondary: Evaluate change from baseline in: 1. QMG total score for disease severity 2. the two most affected QMG individual test items 3. MGFA-PIS 4. MG-ADL 5. respiratory function tests including spirometry to characterize the degree of involvement of respiratory muscles 6. QoL (SF-36).	Randomized, double-blind, placebo-controlled, cross-over, multi-center, pilot study	Double-blind Induction Phase: eculizumab IV or equivalent volume of placebo; 2 vials (600 mg IV) weekly for 4 weeks, then 3 vials (900 mg IV) on the 5th week Double-blind Maintenance Phase: Eculizumab or equivalent volume of placebo; 3 vials; (900 mg IV) every2 weeks for 6 doses.	14 treated and evaluated for efficacy and safety; 13 evaluated for PK and PK/PD eculizumab: n=13 placebo: n=13	Refractory gMG	30-day Screening Period. Two 16-week Treatment Periods separated by a 5-week washout period Follow-up phone call 35 days after last infusion Per patient: Total exposure to eculizumab: up to 16 weeks Total exposure to placebo; up to 16weeks	Study completion 16 Mar 2011 (last patient last visit) Full CSR (C08-001 CSR) Efficacy data are also provided in Module 2.7.3. Safety data are also provided in Module 2.7.4.

Abbreviations: CSR = clinical study report; gMG = generalized myasthenia gravis; IP = investigational product; IV = intravenous; mg = milligrams; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite score; MGFA-PIS = Myasthenia Gravis Foundation of America Post-Intervention Status; PD = pharmacodynamic; PE = plasma exchange; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis score; QoL = quality of life; SF-36 = Short Form-36 Health Survey; TEAEs = treatment-emergent adverse events

6.2. Review Strategy

I will conduct both the primary efficacy and safety reviews for this application. The review is based on clinical trials 301, 302, and CN-08-001. Safety will be based primarily on 301 and 302, with Section 6 of the package insert being based on the 301 trial.

7 Review of Relevant Individual Trials Used to Support Efficacy

7.1. Study Title ECU-MG-301: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Eculizumab in Subjects with Refractory Generalized Myasthenia Gravis (gMG)

7.1.1. Study Design

Overview and Objective

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

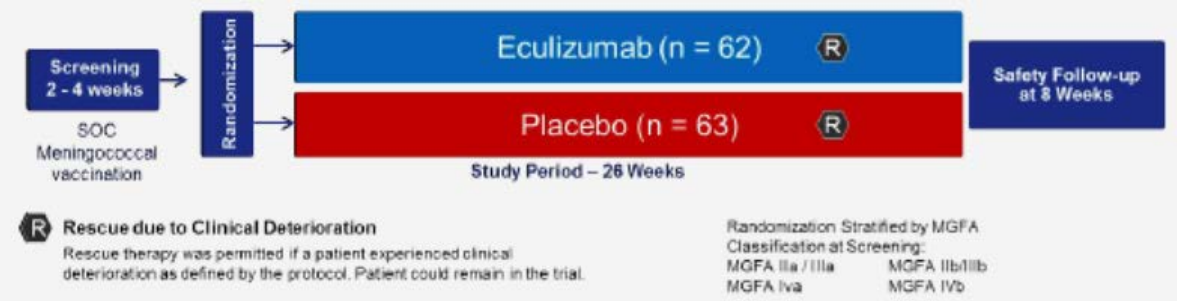
Secondary Objectives – Characterize the overall safety and tolerability of eculizumab as compared with placebo in refractory gMG patients

- Assess the efficacy of eculizumab as compared with placebo by additional efficacy measures including:
  - Quantitative Myasthenia Gravis (QMG) score
  - Myasthenia Gravis Composite (MGC) 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 pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in refractory gMG patients

Trial Design

- *Basic study design* (**Figure 1**)*:*
  - Randomized, double-blind, parallel-group, placebo-controlled, multicenter trial
  - There are three 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 [Study ECU-MG-302]).
  - Twenty-six (26) week on treatment 'Study Period' with option to enter extension study

Figure 1 Schematic Diagram of the Study Design of ECU-MG-301



- *Choice of control group:* Placebo

- *Diagnostic criteria:*

  - Positive serologic test for anti-acetylcholine receptor antibodies as confirmed at Screening, and
  - One of the following:
    - History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation;
    - History of positive anticholinesterase test (eg, edrophonium chloride test); or
    - Patient demonstrated improvement in MG signs on oral cholinesterase inhibitors, as assessed by the treating physician

- *Key inclusion/exclusion criteria:*

Inclusion

1. Male or female patients ≥18 years of age
2. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV at Screening
3. MG-ADL total score ≥6 at Screening and at Randomization (Day 1)
4. 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 [persistent weakness, experienced crisis, or unable to tolerate IST]; or
   b. Failed at least 1 IST and required chronic plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (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, azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate (MTX), cyclosporine (CYC), tacrolimus (TAC), or cyclophosphamide.

5. If patients who entered the study were receiving AZA, they were required to have been on AZA for ≥6 months and on a stable dose for ≥2 months prior to Screening.
6. If patients who entered the study were receiving other ISTs (ie, MMF, MTX, CYC, TAC, or cyclophosphamide), they were required to have been on the IST for ≥3 months and to have been on a stable dose for ≥1 month prior to Screening.
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

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. Any systemic bacterial or other infection that was clinically significant in the opinion of the Investigator and had not been treated with appropriate antibiotics
6. Unresolved meningococcal infection
7. Use of IVIg within 4 weeks prior to Randomization (Day 1)
8. Use of PE within 4 weeks prior to Randomization (Day 1)
9. Use of rituximab within 6 months prior to Screening

- *Rationale for Dose selection [per the applicant]:*

  - PK data from the 14 gMG patients in Study C08-001 were pooled with that from 177 PNH patients to assess PK parameters. The resulting population PK modeling showed mean predicted PK parameters of eculizumab in patients from Study C08-001 treated with the test dosing regimen (900 mg/1200 mg) that were 1.5 and 1.33-fold higher than those observed following administration of the reference dosing regimen (600 mg/900 mg) during the Induction and Maintenance Phases, respectively. PK Simulation studies were reported to suggest that the probability of Cmin being <50 μg/mL decreased from 20.1% to 9.7% for a gMG patient with an average weight of 70 kg [with this dosing regimen].

  - Selection of the 900 mg/1200 mg dosing regimen for the Phase 3 refractory gMG studies was also based on data from the aHUS clinical studies, which suggested that serum eculizumab concentrations greater than 50 μg/mL and closer to at least 100 μg/mL are required to significantly inhibit hemolytic activity to near zero. Minimum eculizumab serum concentrations of 50-100 μg/mL seem needed for essentially "complete and sustained inhibition of hemolytic activity in all aHUS patients". "Overall, significant and sustained terminal complement inhibition as measured by the validated PD assay measuring hemolytic activity" was reportedly demonstrated in all aHUS patients who had achieved a serum concentration of eculizumab >100 μg/mL.

- *Study treatments:*

- Regimen
  - Induction Period: Patients received either eculizumab 900 mg or matching placebo via intravenous (IV) infusion once a week (every 7 ± 2 days) for 4 weeks followed by eculizumab 1200 mg or matching placebo for the fifth dose.
  - Maintenance Period: Patients received either eculizumab 1200 mg or matching placebo via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose onwards.
  - Supplemental Doses: If plasmapheresis or PE was administered as rescue therapy due to clinical deterioration, supplemental study drug (2 vials, equivalent to 600 mg of eculizumab or matching placebo) was administered within 60 minutes after the end of each plasmapheresis/PE session. If plasmapheresis/PE was administered on a day of regularly-scheduled study drug administration, patients received the regularly-scheduled number of vials within 60 minutes after each plasmapheresis/PE session

- Assignment to treatment: Randomized 1:1 to receive either eculizumab or placebo. Approximately 92 patients were planned to be randomized at approximately 100 centers, with 46 patients randomly assigned to eculizumab and 46 patients randomly assigned to placebo. The randomization stratification was based on the assessment of clinical classification by the MGFA performed at the Screening Visit according to the following 4 groupings (see Appendix 14.1.1 for a description of MGA levels):
  - MGFA Class IIa and IIIa
  - MGFA Class IVa
  - MGFA Class IIb and IIIb
  - MGFA Class IVb

- *Concurrent medications*:

- Cholinesterase inhibitors
  - For patients who entered the study receiving a cholinesterase inhibitor at Screening, the dose and schedule of their cholinesterase inhibitor should have been maintained throughout the entire Study Period, unless there was compelling medical need for adjustment of their cholinesterase therapy.
  - Increases in cholinesterase therapy that were required as a result of intercurrent illness or other medical cause of deterioration were permitted, but dosing should have returned to dosing levels at the start of randomized treatment (Baseline) as soon as feasible, and Alexion should have been notified of the change.
  - Cholinesterase inhibitor treatment was required to be withheld for at least 10 hours prior to QMG and MGC assessments.
  - If a decrease in cholinesterase inhibitor was considered based on clinical evaluation, Alexion approval was to be obtained prior to the change in dose in order for the patient to remain on study.

- Immunosupressive therapies
  - The following ISTs were allowed during the study:
    - Corticosteroids
      - For patients who entered the study receiving an oral corticosteroid (eg, prednisone), the dose/schedule could not be changed during the entire double-blind Study Period unless it was deemed medically necessary. If a decrease or taper in steroid dose was considered during the Study Period based on clinical evaluation, Alexion approval was to be obtained prior to the change in order for the patient to remain on study. If the dose level had to be increased subsequently, the dose level increase could not have been above the dose level reported at Baseline (at the start of randomized treatment).
    - Azathioprine (AZA)
    - mycophenolate mofetil (MMF)
    - methotrexate (MTX)
    - tacrolimus (TAC)
    - cyclosporine (CYC)
    - Cyclophosphamide

    For patients who entered the study receiving AZA, MMF, MTX, TAC, CYC, or cyclophosphamide, the dose regimen of the IST may not have been changed during the entire double-blind Study Period. If a change in the dose regimen was considered due to known toxicity or side effects associated with the given IST, Alexion approval was to be obtained prior to the dose change in order for the patient to remain on the study. The study protocol did not permit a different IST to be added or substituted during the 26-week double-blind Study Period.

- Plasmapheresis/IVIG/Plasma Exchange
  - Use of plasmapheresis/PE or IVIg was allowed for patients who experienced clinical deterioration during the study. The rescue therapy used for a particular patient was at the discretion of the Investigator.

Study Endpoints

- *Primary Endpoint*

- Change from Baseline in the MG-ADL total score at Week 26 of the Study Period for eculizumab compared with placebo
  - 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). These 8 items are not weighted and are individually graded from 0 (normal) to 3 (most severe), providing a total score ranging from 0 to 24 points. The MG-ADL

is typically patient-reported; however, in this study, the assessment was performed by a trained and certified clinical evaluator.

- Primary Analysis (Statistical Analysis Plan 13 June 2014 (Version 2.0) used in place of September 23, 2015, Version 3.0): Sponsor's historical accounting for the different versions of the SAP

  - Population definitions
  - 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 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). Patients were assessed for safety according to the treatment they actually received.

The statistical analysis plan (SAP) was updated twice after feedback from the Division (though the final version, v. 3 was not entirely based on this feedback), the details of which are described below. The original SAP and the following amendments include:

- SAP Version 1.0 (approved on 26 Jun 2014)
- SAP Version 2.0 (approved and superseded SAP Version 1.0 on 03 Mar 2015)
- SAP Version 3.0 (approved and superseded SAP Version 2.0 on 23 Sep 2015)

The SAP (Version 1.0) was initially submitted to the FDA in Nov 2014, and the Agency responded with questions and feedback in Jan 2015. The initial primary efficacy analysis (SAP Version 1.0) was Change from Baseline at Week 26 for MG-ADL based on a Worst-Rank ANCOVA analysis. In this analysis, patients requiring rescue therapy were assigned the worst ranks based on time from first dose in the study to the time of rescue event, while all other patients had higher ranks that were based on MG-ADL changes from Baseline to Week 26, with last observation carried forward (LOCF) for those patients without a Week 26 assessment.

Between Jan 2015 and Jan 2016, during the conduct of the ECU-MG-301 Phase 3 study, Alexion and FDA exchanged written correspondence on specifics of the study's SAP. Selection of the Worst-Rank analysis of covariance (ANCOVA) was intended to adjust for the influence of rescue medication on subsequent efficacy assessments. In response to an FDA query on handling patients who dropped out before Week 26 for all potential reasons but were not evaluated with respect to the need of rescue therapy even though they might, in fact, have met the criteria for rescue, Alexion proposed a SAP revision (SAP Version 2.0). This SAP included a Worst-Rank ANCOVA sensitivity analysis that included discontinuation patients in the Worst- Rank rescue cohort who met the protocol-defined criteria for clinical deterioration, although they did not receive rescue treatment. Similar to rescue patients, the rank of these discontinuation patients was based on time from first dose in the study to when they met the protocol-defined criteria for clinical deterioration. Discontinuation patients who did not meet the protocol-defined clinical deterioration criteria would be ranked based on MG-ADL changes from Baseline to Week 26,

with LOCF for those patients without a Week 26 assessment.

In response to SAP Version 2.0, FDA:
(1) noted that the clinical deterioration criteria may not account for patients with respect to the need of rescue therapy even though they might, in fact, have met the criteria for rescue; (2) asked whether there would be one or more than one sensitivity analysis with these criteria; (3) agreed that last available observation and LOCF would be the same in this study; (4) recommended that to detect the impact of using different ranking scales in the sensitivity analyses, the same ranking scale should be used for both the patients who need rescue therapy and those who drop out without rescue in the primary and sensitivity analyses; and (5) proposed clarification of ranking of the different clinical worsening scenarios in the rescue group in the proposed sensitivity analysis. FDA concluded its response by emphasizing that a high proportion of rescues or dropouts could make the analyses uninterpretable.

Following the above interaction with FDA and prior to locking the clinical database and unblinding the study, Alexion further amended the SAP (SAP Version 3.0), which clarified the ranking of clinical worsening within the discontinued patients in the primary analysis (instead of in the sensitivity analysis), but now also included ***all discontinued patients***, irrespective of whether they met the clinical deterioration criteria or not, in the primary analysis, as opposed to the earlier proposed handling of dropouts in the proposed sensitivity analysis. This last revision to the primary analysis ***assigned all discontinued patients to be ranked within the rescue therapy cohort, regardless of known improvement or deterioration on clinically-validated MG outcomes.***

In the SAP v.3 Worst-Rank ANCOVA, patients who died would get the worst ranks based on time from the first dose of study drug to death date. Then, patients experiencing myasthenic crisis would be ranked based on time from the first dose of study drug to myasthenic crisis. Then, patients needing rescue therapy for significant symptomatic worsening to a score of 3 or a 2-point worsening on any 1 of the individual items other than double vision or eyelid droop, or patients whose treating physician believed that the patient's health would be in jeopardy if rescue therapy was not given (e.g., emergent situations), together with patients who discontinued but did not receive rescue therapy, would be assigned the next worst ranks. All other patients who completed Week 26 without the use of rescue therapy were ranked based on their changes from Baseline, or LOCF if Week 26 was missing.

- 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 (e.g., emergent situations).

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. 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.

Primary Sensitivity Analysis
A Worst-Rank ANCOVA sensitivity analysis was performed to compare the 2 treatment arms. In this sensitivity analysis, the actual change from Baseline in the MG-ADL total score at Week 26 was calculated for all patients who completed 26 weeks on study treatment without rescue therapy. For patients who completed the 26-week study but were missing Week 26 values, the LOCF was used. For patients who received rescue therapy or discontinued the study, the LOCF was used prior to rescue medication use, or time of discontinuation. Importantly, this sensitivity analysis retained the assignment of all rescue patients and discontinuation patients to the lowest ranks (ie, ranked lower than patients who completed the 26-week study without rescue or discontinuation).

Other sensitivity analyses

- 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 randomization stratification variable;
- Repeated Measures over time accounting for treatment arm, Baseline score, randomization stratification variable, and visit; and
- Repeated Measures over time accounting for treatment arm, Baseline score, randomization stratification variable, visit, and IST impact.

Medical Officer's Comments: In the Statistical Analysis Plan (SAP) Version 3.0, all patients who discontinued from the study were assigned to the worst ranks, regardless of clinical outcome. This approach risks inappropriately imputing a poor outcome to patients who responded well to the study drug and discontinued for reasons unrelated to efficacy. The primary endpoint is also presented based on SAP Version 2.0, which specified an alternative approach for the Worst-Rank assignments. In SAP Version 2.0, patients who received rescue therapy and who experienced a clinical deterioration as defined by the study protocol (with or without rescue therapy) were assigned the worst ranks, and patients who discontinued from the study without clinical deterioration were ranked according to their last assessment using a last-observation carried forward approach. Another analysis was performed based on a modification to the Worst-Rank approach specified in SAP Version 2.0, in which patients who experienced myasthenic crisis during the study were given the worst rank and were followed by patients who experienced a protocol-defined clinical deterioration but not myasthenic crisis. **I concur with the applicant's position that SAPv.2 is the most sensible analysis from a clinical perspective.**

- *Secondary Endpoints (hierarchical)*

  - (1) Change from Baseline in the QMG total score at Week 26
    - 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). These 13 items are objectively and quantitatively assessed and each graded from 0 to 3, with 3 being the most severe, providing a total QMG score ranging from 0 to 39

  - (2) Proportion of patients with ≥3-point reduction in the MG-ADL total score from Baseline to Week 26 and with no rescue therapy

  - (3) Proportion of patients with ≥5-point reduction in the QMG total score from Baseline to Week 26 and with no rescue therapy

  - (4) Change from Baseline in the MGC scale total score at Week 26
    - The MGC score is a 10-item (2 to 6 points per item) a hybrid of physician- and patient-reported test items and is weighted to account for the potential clinical impact of MG signs and symptoms. Possible cumulative scores range from 0 to 50, with higher scores representing greater morbidity.

  - (5) Change from Baseline in the Myasthenia Gravis Quality of Life 15-item Scale (MG-QoL15) at Week 26
    - The Myasthenia Gravis Quality of Life 15-item scale (MG-QoL15) is a validated disease specific questionnaire 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

- Statistical Analysis of Secondary Endpoints

The hypothesis testing proceeded from the first secondary hierarchical endpoint (change from Baseline in QMG total score at Week 26) to the fifth secondary hierarchical endpoint (change from Baseline in MG-QoL15 at Week 26). If statistical significance was not achieved for an endpoint ($p \leq 0.05$), then all endpoints of lower hierarchy were also not considered statistically significant, regardless of the calculated p-value. The closed testing procedure was only used for the main analysis of each of the secondary efficacy endpoints; sensitivity analyses were not part of the closed testing procedure.

The secondary endpoints that involve changes from baseline (i.e. QMG, MGC, and MG-QOL15) were analyzed using a worst-case ranked analysis of covariance (ANCOV A) like that described for the primary efficacy endpoints as the primary analysis for the particular secondary endpoint. The ranked ANCOV A had effects for treatment, the baseline for the particular endpoint, and the randomization stratification variable.

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

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

- *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 Quality of Life in Neurological Disorders Fatigue at Week 26
  - Change from Baseline in the European Quality of Life Health Questionnaire at Week 26
  - Change from Baseline in Negative Inspiratory Force (NIF) at Week 26 in patients with abnormal NIF at Baseline
  - Change from Baseline in Forced Vital Capacity (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 Post-Intervention Status at Week 26.

- *Pharmacokinetics and Pharmacodynamics:*

  - Assessment of PK and PD parameters during the induction and maintenance phases of treatment

Protocol Amendments

The applicant had one major amendment to the protocol for ECU-MG-301 Version 1.0 dated 15 August 2013 that was Protocol Amendment 3 Protocol Version 2.0- 13 June 2014. I have reviewed this amendment and do not believe any of the changes would substantially change the outcome of the study.

Changes in the Conduct of the Study Not Specified in an Amendment

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 MG (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 MG (n = 25 patients)

Specific records in the clinical database were unlocked for a total of 7 patients to address the identified inconsistencies.

This event is discussed in the context of the OSI inspection that followed identification of the database unlocking (see Section 5.1.2 Sponsor inspection).

7.1.2. Study Results

Financial Disclosure

All of the financial disclosure forms submitted with the BLA were reviewed. Two investigators indicated that they had received grants or honoraria from Alexion, in the 301 trial, (b) (6) and in 302, (b) (6) from (b) (6). Evaluation of the randomization data and efficacy results suggested that they did not influence the outcome of the trial (see also Section 14.2 Financial Disclosure).

Patient Disposition

126 patients were randomized (Table 5), 125 were treated (1 randomized in error did not receive treatment). Eight (6.3%) subjects discontinued, 2(3.2%) in the placebo group and 6 (9.5%) in the eculizumab arm. Four (4(6.3%)) eculizumab subjects[1] discontinued due to adverse events, one (1(1.6%)) withdrew consent[2], and one[3] (1(1.6%)) was randomized in error and did not receive drug (classified as 'Other'). The reason for discontinuation for the subjects in the placebo arm[4] was listed as 'Withdrawal by subject' (Table 5).

The effect of the eculizumab-treated patients who had discontinued the study but did not show signs of clinical deterioration when considering SAP V. 2 versus v. 3 is described in later in this section (see Figure 3).

[1] AE d/c Subject #s (b) (6), (b) (6), (b) (6), (b) (6)
[2] W/D consent Subject # (b) (6)
[3] Subject# (b) (6)
[4] Placebo D/C Subject #s (b) (6) and (b) (6), both received rescue therapy

Table 5 Disposition of Subjects in Study ECU-MG-301

Status	Placebo n (%)	Eculizumab n (%)	Total N (%)
Randomized	63 (100.0)	63 (100.0)	126 (100.0)
Treated	63 (100.0)	62 (98.4)	125 (99.2)
Completed the Study	61 (96.8)	57 (90.5)	118 (93.7)
Discontinued	2 (3.2)	6 (9.5)	8 (6.3)
Adverse Event	0 (0.0)	4 (6.3)	4 (3.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by Patient	2 (3.2)	1 (1.6)	3 (2.4)
Other	0 (0.0)	1 (1.6)	1 (0.8)
Enrolled in Open-Label Extension Study (Study ECU-MG-302)	61 (96.8)	56 (88.9)	117 (92.9)

Note: Percentages are based on the number of randomized patients in each column.
Source: Table 14.1.2.3.5

Source - Clinical Study Report ECU-MG-301, Table 6, p. 78 of 208

Protocol Violations/Deviations

Patients who had major protocol deviations included:

- Not having a stable dose of IST therapy at the time of enrollment and/or having a change in IST status during the study (5 patients from the placebo arm and 7 patients from the eculizumab arm).

Medical Officer's Comments: I have reviewed the cases described by the applicant and after having considered the time between the medication changes and randomization and the distribution between arms do not believe this would have affected the interpretation of the trial outcome.

- Patient (b) (6); placebo arm had an MG-ADL assessment performed by himself instead of by a trained evaluator,
- Patient (b) (6); placebo arm had a compliance with the study drug that was <80%,
- Patient (b) (6); eculizumab arm required emergency unblinding during the study

Medical Officer's Comments: I have reviewed the cases described by the applicant and do not believe these would have affected the interpretation of the trial outcome.

Table of Demographic Characteristics

Demographics were generally balanced between eculizumab and placebo arms with the exception of the following factors:

- Race – There is a disproportionate amount of Asian patients in the placebo (16(25.4)) versus the eculizumab arm (3(4.8)).
- Exacerbations – There is an imbalance in the number of subjects wit total reported exacerbations between the placebo (316 (82.5%)) and eculizumab (206(74.2%) arms.
- History of Thymectomy - There is an imbalance in the number of subjects with a history of thymectomy between the placebo (31 (49.2%)) and eculizumab (37 (59.7%)) arms.

These factors were evaluated as covariates for the primary endpoint and determined, in my evaluation, not to be significant factors in the outcome (c.f., Figure 6)

Patient demographics and clinical characteristics are presented in Table 6 and Table 7, respectively.

- Concomitant Medications

Concomitant medications at baseline and through the trial were generally balanced between treatment groups.

- The most common ISTs used ***prior to*** enrollment into the study were corticosteroids (120 [96.0%] patients overall; 62 [98.4%] patients in the placebo arm and 58 [93.5%] patients in the eculizumab arm) and AZA (94 [75.2%] patients overall; 47 [74.6%] patients in the placebo arm and 47 [75.8%] patients in the eculizumab arm).
  - 48 [76.2%] patients in the placebo arm and 51 [82.3%] patients in the eculizumab arm) had received prior IVIg therapy, and about half of patients (60 [48.0%] patients overall; 29 [46.0%] patients in the placebo arm and 31 [50.0%] patients in the eculizumab arm) had received prior PE.
- The most commonly used classes of concomitant medications ***during the study*** were
  - anticholinesterases (111 [88.8%] patients overall; 53 [84.1%] patients in the placebo arm and 58 [93.5%] patients in the eculizumab arm),
  - corticosteroids (100 [80.0%] patients overall; 51 [81.0%] patients in the placebo arm and 49 [79.0%] patients in the eculizumab arm), and
  - proton pump inhibitors (66 [52.8%] patients overall; 33 [52.4%] patients in the placebo arm and 33 [53.2%] patients in the eculizumab arm).
- Immunosuppressive therapy other than prednisone was used during the study by 52 (82.5%) patients in the placebo arm and 55 (88.7%) patients in the eculizumab arm.
- Specific concomitant medications for any indication used by more than 25% of patients overall include (listed by decreasing overall incidence):
  - pyridostigmine bromide - 37 [58.7%] patients in the placebo arm and 38 [61.3%] patients in the eculizumab arm),
  - prednisone - 26 [41.3%] patients in the placebo arm and 26 [41.9%] patients in the eculizumab arm),
  - AZA - 21 [33.3%] patients in the placebo arm and 20 [32.3%] patients in the eculizumab arm),
  - MMF- 16 [25.4%] patients in the placebo arm and 18 [29.0%] patients in the eculizumab arm), and
  - pyridostigmine - 15 [23.8%] patients in the placebo arm and 18 [29.0%] patients in the eculizumab arm).

Table 6 Demographics of Patients in Study 301

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)

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/m^2) = Weight (kg) / [Height (cm) / 100]^2
Abbreviations: BMI = body mass index; IP = investigational product; MGFA = Myasthenia Gravis Foundation of America; SD = standard deviation
Source: Table 14.1.1.1.1

Source - Clinical Study Report ECU-MG-301, Table 7, pp. 83-4 of 208

Table 7 Baseline Clinical Characteristics by Randomized Treatment

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; SD = standard deviation

Source: Table 14.1.3.2.1, Table 14.1.3.5.1, Table 14.2.1.3.1, Table 14.2.2.3.1.2, Table 14.2.2.31.1.2, Table 14.2.2.51.1.2

Medical Officer's Comments: I evaluated several demographic characteristics for imbalances between treatment groups. These included AGE, SEX, RACE, ETHNIC, COUNTRY, REGION, JAPANDSC (Japanese descent), ISTDAY1 (baseline immunosuppressive therapy), and MGFAST (baseline MG Functional Activity Status category). **None of the factors showing differences (described below) at baseline were significantly associated in regression or chi-square analyses of change from baseline of the MGADL, but are included below to inform what was considered.**

Differences at baseline were noted with respect to RACE (nominal P = 0.0022 Likelihood ratio (LR)); this was likely due to an imbalance of Asian patients in the eculizumab (N = 3) versus placebo (N = 16) group ad African-Americans, where there were 0 patients in the eculizumab group and 3 in the placebo group. Imbalances were also noted in the number of subjects by COUNTRY (nominal P=0.0041 LR), particularly in Czechoslovakia (N = 5 eculizumab, 0 placebo), Hungary (4, 0), Italy (6, 1), and Korea 0, 5). REGION differences (nominal P=0.006 LR) reflected the findings by country. Baseline immunosuppressive therapy differences were significant by this analysis (nominal P = 0.0026), driven by differences in the difference of baseline score of those on prednisone alone or no IST in the eculizumab group (N = 7, median = 11) compared to those on placebo (N = 11, median 8).

Efficacy Results – Primary Endpoint

When analyzed per the final version of the Statistical Analysis Plan (Version 3.0), the primary outcome measure did not reach statistical significance (Table **8**; see a discussion of the SAPs in Section 7.1.1). This version of the SAP required assignment of the Worst Ranking if subjects discontinued or took rescue medication, irrespective of whether they showed clinical deterioration or not.

Table 8 Primary Outcome Measure Analysis: MG-ADL Total Score per SAP v. 3

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		

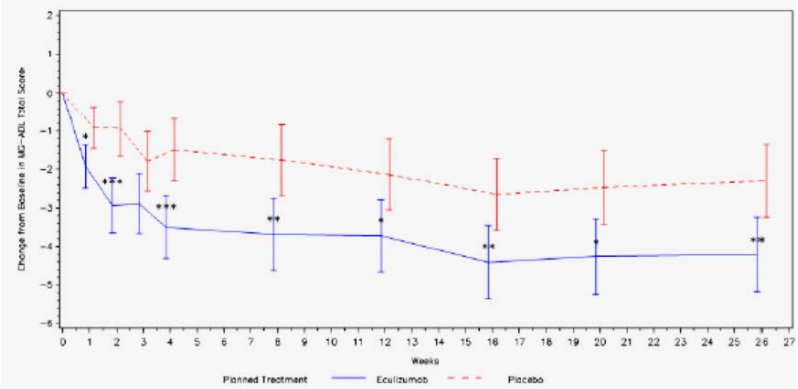
The applicant also analyzed the data using the conventions from version 2, where patients who discontinued were given a Worst Ranking only if they showed clinical deterioration or took rescue medications. Analysis of the data using these conventions is presented in Table 9. Graphic demonstration of the change from baseline using a repeated measures analysis is in Figure 2.

Table 9 Primary Outcome Measure Analysis: MG-ADL Total Score per SAP v. 2

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Change from Baseline (1)	LS Mean (SEM)	-2.6 (0.48)	-4.0 (0.48)	-1.4	0.0390
	95% CI for LS Mean	(-3.52, -1.63)	(-4.96, -3.04)	(-2.77, -0.07)	
Baseline MG-ADL Total Score	n	63	62		
	Mean (SD)	9.9 (2.58)	10.5 (3.06)		
	Median	9.0	10.0		
	Min, Max	5, 18	5, 18		
Week 26 MG-ADL Total Score (LOCF)	n	63	62		
	Mean (SD)	7.4 (3.50)	6.4 (4.76)		
	Median	7.0	6.0		
	Min, Max	0, 16	0, 17		
Change from Baseline to Week 26 in MG-ADL Total Score	n	63	62		
	Mean (SD)	-2.4 (3.32)	-4.1 (4.48)		
	Median	-2.0	-4.0		
	Min, Max	-8, 7	-15, 4		

(1) LS Means are from the ANCOVA model.
Note: p-value from ANCOVA analysis of change from baseline, testing for the effect of treatment, with the baseline value and the pooled MGFA randomization stratification variable as covariates in the model. For patients who did not require rescue therapy, if the Week 26 MG-ADL total score was missing or an item from the Week 26 MG-ADL was missing, last observation carried forward (LOCF) was used for missing Week 26 MG-ADL total score or missing item was missing or an item from the Week 26 MG-ADL was missing, last observation carried forward (LOCF) was used for missing Week 26 MG-ADL total score or missing item of the Week 26 MG-ADL. For patients requiring rescue therapy, the last observation prior to the first use of rescue therapy was used. If the last observation prior to the first use of rescue therapy was missing an item from the MG-ADL, last observation carried forward was used for the missing item.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Max = maximum; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGFA = Myasthenia Gravis Foundation of America; Min = minimum; SD = standard deviation; SEM = standard error of the mean
Source: Table 14.2.1.19.1

Figure 2 Change from Baseline in the MG-ADL Treatment Using a Repeated Measures Model



The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, and the MG-ADL total score at baseline. Missing MG-ADL total score values were not imputed.
*, **, and *** to represent the two-sided nominal p-value for the comparison of treatment arms in change from Baseline in the MG-ADL total score by visit using Repeated-Measures model is less than 0.05, 0.01, and 0.001, respectively.
Abbreviations: CI = confidence interval; LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGFA = Myasthenia Gravis Foundation of America
Source: Figure 14.2.1.1.1

The SAP v.2 analysis could have potentially affected the rank analysis (relative to version 3) of 4 subjects based on their rescue medication and clinical deterioration status (Table 10). None of

the 4 took rescue medications. Subject (b) (6) demonstrated a clinical deterioration so would have received a higher rank with either version; there isn't a notable difference in the imputed results. Three of the 4 patients on eculizumab discontinued due to adverse events but did not show signs of clinical deterioration and so are not ranked as low when the data is analyzed by v.2 versus v.3.

Table 10 Worst Rank Assignments for Patients with Assignment based on SAP Version

Patient Number	Treatment arm	Cohort for Rank Assignment	Rank in SAP Version 3.0 (1)	Rank in SAP Version 2.0 (2)	Rank in SAP Version 1.0 (3)
(b) (6)	Ecultzumab	MG Crisis	125	112	113
	Ecultzumab	Rescue	124	125	125
	Placebo	Rescue	123	124	124
	Placebo	Rescue	122	123	123
	Placebo	Rescue	120.5	120.5	121.5
	Placebo	Rescue	120.5	120.5	121.5
	Ecultzumab	Rescue	119	119	120
	Placebo	Rescue	118	118	119
	Eculizumab	**Discontinuation**	**117**	**122**	**60**
	Placebo	Rescue	116	117	118
	Placebo	Rescue	115	116	117
	Placebo	Rescue	114	115	116
	Placebo	Rescue	113	114	115
	Eculizumab	**Discontinuation**	**112**	**59.5**	**60**
	Eculizumab	**Discontinuation**	**111**	**22.5**	**22.5**
	Ecultzumab	Rescue	110	113	114
	Eculizumab	**Discontinuation**	**109**	**22.5**	**22.5**
	Placebo	Rescue	108	111	112
	Placebo	Rescue	107	110	111
	Ecultzumab	Rescue	106	109	110
	Ecultzumab	Rescue	105	108	109
	Placebo	Rescue	104	107	108

Note: Rows shown in bold indicate patients who were in the Discontinuation cohort; rows shaded in grey indicate patients included in the Discontinuation cohort who did not fulfill protocol-defined criteria for MG clinical deterioration.
(1) SAP Version 3.0 became effective and superseded SAP Version 2.0 on 23 Sep 2015.
(2) SAP Version 2.0 became effective and superseded SAP Version 1.0 on 03 Mar 2015.
(3) SAP Version 1.0 became effective on 26 Jun 2014.
Abbreviations: MG = myasthenia gravis; SAP = statistical analysis plan
Source: Listing 16.2.6.1.2.1, Listing 16.2.6.1.2.1.1, Listing 16.2.6.1.2.1.2

Medical Officer's Comments: I have reviewed the data of all 4 subjects and agree with the applicant on their assertion that SAP v. 2 is more clinically appropriate than v.3 for the primary analysis. A time course of performance on several key scales used in Study 301 is demonstrated in Figure 3. In the case of both the MG-ADL and QMG scale, an increase in score represents a worsening of the patient's condition. Subject (b) (6), appropriately, shows an increase in both Scale scores before discontinuing, whereas the scores of other 3 remain fairly stable or improved (Figure 3). In summary, I believe this figure supports use of the SAP v.2 conventions for the primary analysis.

Clinical narratives are included for the 3 subjects not showing clinical deterioration.

Patient (b) (6) had a baseline MG-ADL score of 14 including symptoms of impaired talking, chewing, vision, and swallowing, together with shortness of breath and upper limb weakness. By Week 4 of treatment, her MG-ADL had improved by 5-points, at which time she also received her last eculizumab dose. She had 2 treatment-related SAEs (Moraxella bacteremia and endocarditis), each with onset on (b) (6) and which resolved by (b) (6). Despite concomitant morbidity, **at time of study withdrawal on (b) (6), her MG-ADL score**

remained improved by 3 points compared with Baseline. The patient did not fulfill MG clinical deterioration criteria or receive rescue therapy.

Patient (b) (6) had a baseline MG-ADL score of 13 including symptoms of impaired talking, chewing, vision, and swallowing, together with shortness of breath, upper and lower limb weakness, and facial muscle weakness. At Week 8 of treatment, his MG-ADL score had improved by 6 points. He received his last dose of eculizumab 2 weeks later on (b) (6) and, on (b) (6), he was diagnosed with metastatic adenocarcinoma of the prostate gland. Despite concomitant morbidity, **at time of study withdrawal on (b) (6), the patient's MG-ADL score remained improved by 7 points compared with Baseline**. The patient did fulfill MG clinical improvement criteria and did not fulfill MG clinical deterioration criteria.

Patient (b) (6) had a baseline MG-ADL score of 10 including symptoms of impaired talking, chewing, and swallowing, together with shortness of breath, upper limb weakness, impaired lower limb use, and facial muscle weakness. At Week 12 of treatment, his MG-ADL score had improved by 3 points. He received his last dose of eculizumab 2 weeks later on (b) (6) and withdrew from the study on (b) (6) due to SAEs of worsening diverticulitis and bowel perforation. Despite concomitant morbidity, **his MG-ADL score at the final visit remained improved by 7 points compared to Baseline.** The patient did fulfill MG clinical improvement criteria and did not fulfill MG clinical deterioration criteria.

Table 11 demonstrates that the primary endpoint was consistently positive with other methods of analysis.

Table 11 Sensitivity Analyses of the Primary Endpoint for Study 301

Analysis	Final Analysis with All Discontinuations in Rescue Cohort for Worst-Rank Analysis (p-value) (1)
Worst-Rank ANCOVA (Worst-Rank Sensitivity)	0.0698 (0.0800) (2)
Week 26 ANCOVA Change from Baseline	0.0390
Repeated-Measures at Week 26 (Repeated-Measures including IST as a covariate)	0.0058 (0.0077)
Responder Analysis ≥3-point improvement at Week 26 without rescue (see Section 11.4.1.2.1.2)	0.0229

(1) Nominal p-value
(2) Similar to primary analysis considers both rescue and all discontinuations the same for analytical purposes, but patients in worst rank groups are ranked using actual changes from Baseline using LOCF instead of time from first dose of study drug to event.

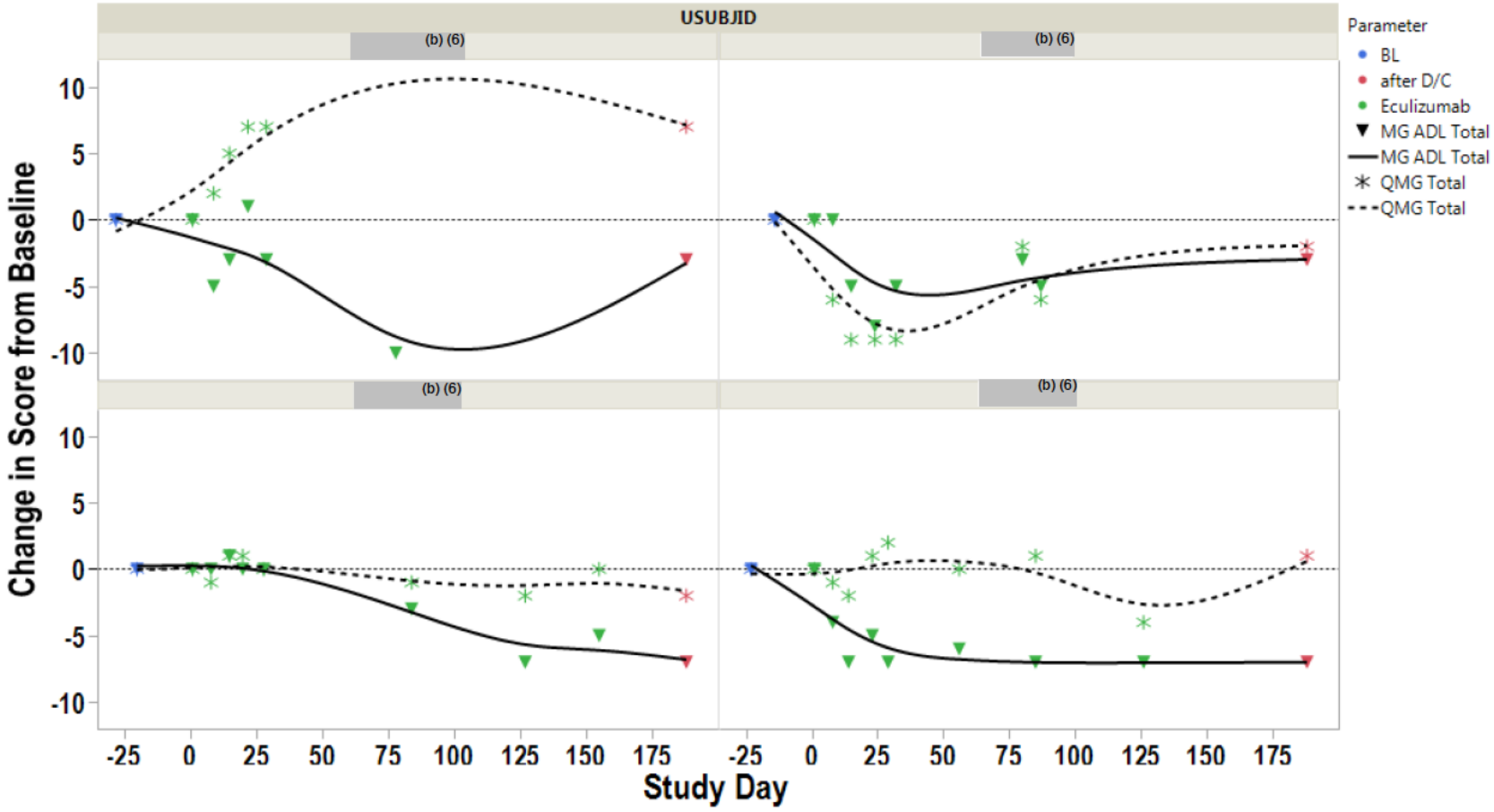
Abbreviations: ANCOVA = analysis of covariance; IST = immunosuppressive therapy; LOCF = last observation carried forward; MG-ADL = Myasthenia Gravis Activities of Daily Living profile

Source: Table 14.2.1.1.1.1, Table 14.2.1.2.1, Table 14.2.1.5.1, Table 14.2.1.19.1, Table 14.2.1.21.1, Table 14.2.2.21.1

Data Quality and Integrity – Reviewers' Assessment

The data quality was adequate for analysis. Data integrity is discussed in Section 5.1.

Figure 3 MG-ADL and QMG Scores for the 4 Subjects Discontinuing Therapy



Efficacy Results – Secondary and other relevant endpoints

In order to account for multiplicity, hypothesis testing comparing eculizumab treatment with placebo treatment for the secondary efficacy analyses was performed using a closed testing procedure with the following rank order:
1. Change from Baseline in QMG total score at Week 26
2. Proportion of patients with at least a 3-point reduction in the MG-ADL total score from Baseline to Week 26 and with no rescue therapy
3. Proportion of patients with at least a 5-point reduction in the QMG total score from Baseline to Week 26 and with no rescue therapy
4. Change from Baseline in the MGC score at Week 26
5. Change from Baseline in MG-QoL15 at Week 26

Hypothesis testing proceeded from (#1) Change from Baseline in QMG total score at Week 26 to (#5) Change from Baseline in MG-QoL15, and if statistical significance was not achieved at an endpoint ($p \leq 0.05$), then endpoints of lower rank would not be considered statistically significant.

Medical Officer's Comments: The analysis reported for secondary endpoints secondary endpoints follows the SAP v.3; this would impact the 'Change' endpoints (endpoints 1, 4, and 5). The Statistical review provides the P Values that result from SAP v. 2 and so these are included in the section that follows in the comments for those endpoints and also in my overall analysis of the secondary endpoints.

Secondary Endpoint #1 – Quantitative Myasthenia Gravis Total Score

A significant difference was noted between treatments in favor of eculizumab in the first secondary outcome measure, the Change from Baseline in the QMG Total Score (Table 12).

Table 12 Change from Baseline in QMG at Week 26: ANCOVA Worst-Rank Score (SAP v.2)

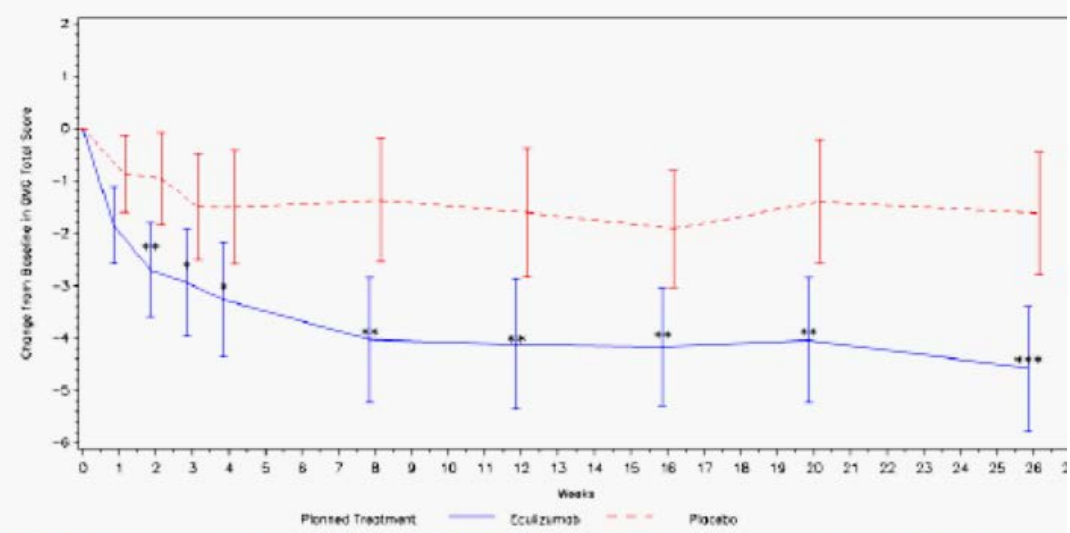
Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Worst-Rank Change from Baseline	Ranked Score LS Mean (SEM)	70.7 (4.46)	54.7 (4.50)	-16.0	0.0129
	95% CI for LS Mean	(61.85, 79.51)	(45.82, 63.64)	(-28.48, -3.43)	
Baseline QMG Total Score for patients not 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		

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Max = maximum; Min = minimum; QMG = Quantitative Myasthenia Gravis score for disease severity; SD = standard deviation; SEM = standard error of the mean

Source: Clinical Study Report ECU-MG-301 p. 95/208

A nominal difference is also demonstrated in other sensitivity analyses of this endpoint (Figure 4 and Table 13).

Figure 4 Change from Baseline in the QMG Total Score to Week 26 by Treatment by Repeated Measures Analysis



*, **, and *** to represent the two-sided nominal p-value for the comparison of treatment arms in change from Baseline in the QMG total score by visit using a Repeated-Measures model is less than 0.05, 0.01, and 0.001, respectively.
Abbreviations: CI = confidence interval; LS = least squares; QMG = Quantitative Myasthenia Gravis score for disease severity
Source: Figure 14.2.2.1.1

Source: Clinical Study Report ECU-MG-301 p. 97/208

Table 13 Summary of QMG Sensitivity Analyses

Analysis	Final Analysis with All Discontinuations in Rescue Cohort for Worst-Rank Analysis (p-value) (1)
Worst-Rank ANCOVA (Worst-Rank Sensitivity)	0.0129 (0.0169) (2)
Week 26 ANCOVA Change from Baseline	0.0032
Repeated-Measures at Week 26 (Repeated-Measures including IST as a covariate)	0.0006 (0.0007)
Responder Analysis ≥5-point improvement at Week 26 without rescue (see Section 11.4.1.2.1.3)	0.0018

(1) Nominal p-value
(2) Similar to primary analysis considers both rescue and all discontinuations the same for analytical purposes, but patients in worst rank groups are ranked using actual changes from Baseline using LOCF instead of time from first dose of study drug to event.
Abbreviations: ANCOVA = analysis of covariance; IST = immunosuppressive therapy; LOCF = last observation carried forward; QMG = Quantitative Myasthenia Gravis score for disease severity
Source: Table 14.2.2.1.1.1, Table 14.2.2.3.1, Table 14.2.2.5.1, Table 14.2.2.19.1, Table 14.2.2.25.1, Table 14.2.2.62.1

Source: Clinical Study Report ECU-MG-301 p. 98/208

According to the finalized Statistical Review, following the SAP v. 2, the QMG showed a significant treatment effect (P = 0.0129)

Secondary Endpoint #2 – Proportion of Patients with at Least a 3-Point Reduction in Myasthenia Gravis Activities of Daily Living Total Score

There was a significantly larger proportion of clinical responders (based on a ≥3-point reduction in MG-ADL total score from Baseline to Week 26 with no rescue therapy) in the eculizumab arm (37 [59.7%] patients) than in the placebo arm (25 [39.7%] patients) (p = 0.0229;Table 14).

Table 14 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

	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)		

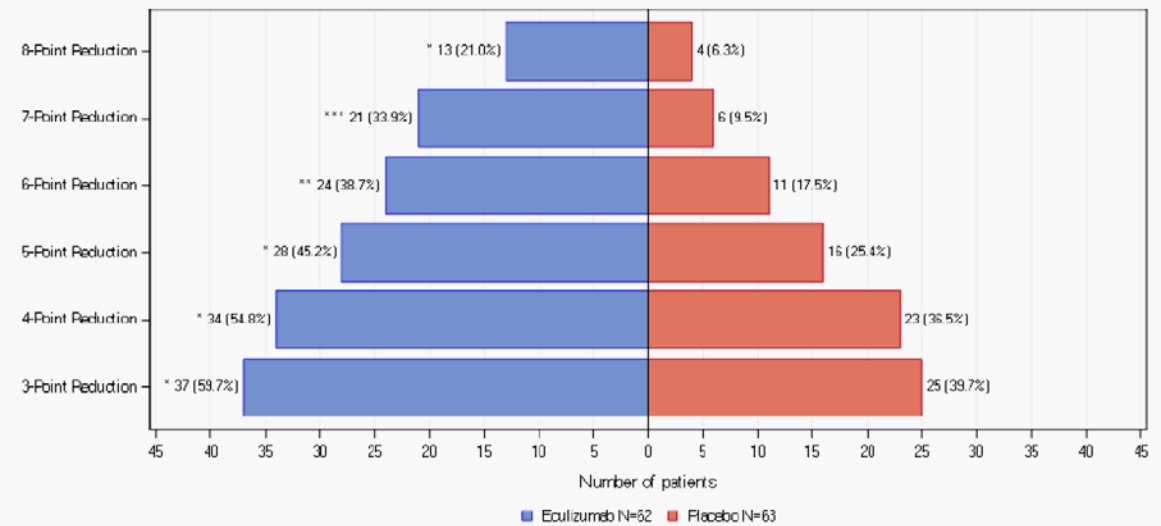
Note: P-value is from a CMH test, testing for a difference in proportions between treatments, adjusting for the pooled MGFA randomization stratification variable.
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; MGFA = Myasthenia Gravis Foundation of America

Source: Clinical Study Report ECU-MG-301 p. 98/208

The number of patients experiencing a ≥3-point reduction through a ≥8-point reduction in MG-ADL total score at Week 26 and no rescue therapy is shown in Figure 5

Figure 5 Proportion of Patients with Different Point Reductions in MG-ADL Total

Score and No Rescue Therapy Assessed at Week 26

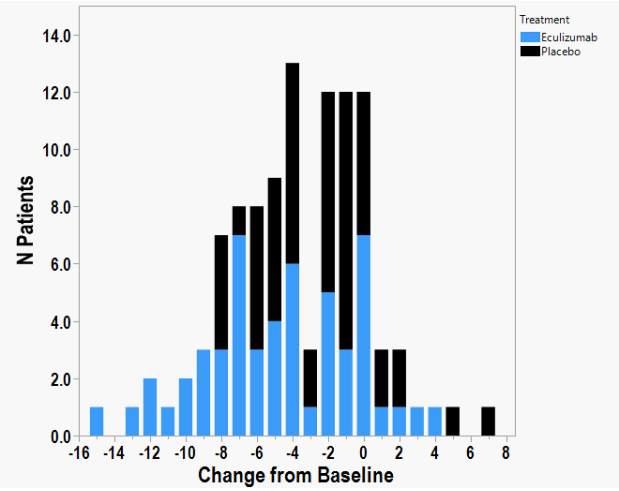


*, *, and *** to represent the two-sided nominal p-value for the comparison of treatment arms in the proportion of patients with different point reductions in MG-ADL total score and no rescue therapy assessed at Week 26 using CMH test is less than 0.05, 0.01, and 0.001, respectively.
Abbreviations: CMH = Cochran-Mantel-Haenszel; MG-ADL = Myasthenia Gravis Activities of Daily Living profile

Source: Clinical Study Report ECU-MG-301 p. 100/208

I have graphically demonstrated the distribution of the Change from Baseline at endpoint for the MGADL by treatment in Figure 6.

Figure 6 Distribution of the Change from Baseline of the MGADL by Treatment



Source: Medical reviewer analysis of MGADLSAP2 as prepared by the review team biostatistician

A categorical analysis was performed to determine if the results in the MGADL responder analysis were significantly associated with any particular demographic factor (e.g., age, sex, country, site, etc…). Responder analyses were performed contrasting the treatments when the

responder definition was -3, -5, and -10 for the change from baseline of the MG ADL (c.f., Figure 7). The latter 2 were nominally significant (P = 0.0175 and 0.0245, respectively) but the change of -3 was not (nominal P = 0.0786 LR) in my analysis. Of all of the factors included in this model, only Treatment showed a significant association.

Figure 7 Responder Analysis of the MGADL at the -5 point Change from Baseline Level

Responses(Responder definition -5) By TRT01A

			Freq / Share / Comparisons	Responder definition -5 N	Responder definition -5 Y	Total Responses
TRT01A	Eculizumab	A		26	27	53
				49.1%	50.9%	
				*	B*	
	Placebo	B		36	15	51
				70.6%	29.4%	
				A*	*	

Default Comparison Groups: A/B

Shows letter of the category it is significantly different from at the higher share level

* Base count warning	100	Uppercase Alpha Level	0.05
** Base count minimum	30	Lowercase Alpha Level	0.1

Share Chart		Responder definition -5 N	Responder definition -5 Y	
TRT01A	Eculizumab			53
	Placebo			51

Test Response Homogeneity

Response Dimension Label	Sample Dimension Label	LR Chisq	LR PValue	Pearson Chisq	Pearson PValue
Responder definition -5	TRT01A	5.05832	0.0245*	5.00486	0.0253*

Secondary Endpoint #3 – 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).

Table 15 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

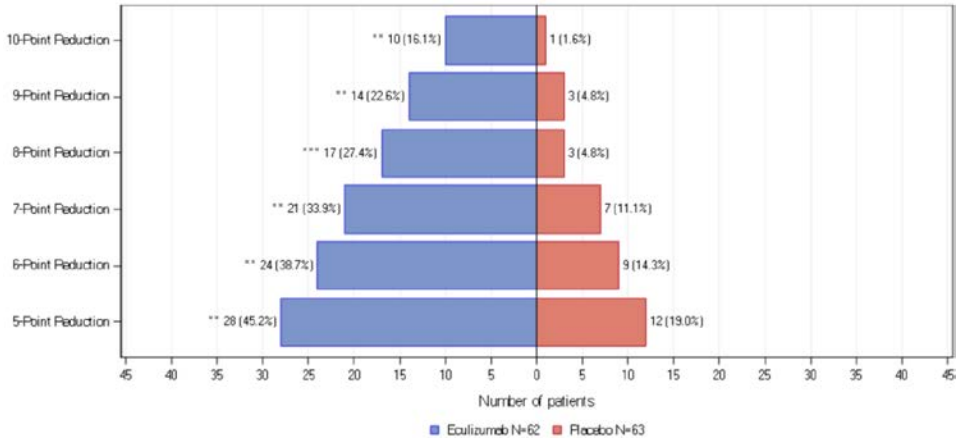
	Statistic	Placebo (N = 63) n/N (%)	Eculizumab (N = 62) n/N (%)	Difference in % (95% CI)	p-value
Overall	n/N (%)	12/63 (19.0)	28/62 (45.2)	26.2 (10.4, 41.8)	0.0018
	95% CI of %	(10.2, 30.9)	(32.5, 58.3)		

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

The number of patients experiencing a ≥5-point reduction through a ≥10-point reduction at Week 26 and no rescue therapy in QMG total score is shown in Figure 8. The proportion of who experienced point reductions of ≥5 points through ≥10 points and no rescue therapy had a p-value of <0.05 using the CMH test after adjusting for the pooled MGFA randomization

stratification variable for the comparison between treatment arms, favoring eculizumab at all thresholds of point reduction.

Figure 8 Proportion of Patients with Different Point Reductions in QMG Total Score and No Rescue Therapy Assessed at Week 26



Source: Clinical Study Report ECU-MG-301 p. 101/208

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, presented in Table 14.2.1.31.1 for the FAS and Table 14.2.1.31.2 for the PP Set.
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.

Secondary Endpoint #4 – Myasthenia Gravis Composite Total Score

The Myasthenia Gravis Composite total score was not positive using the analysis according to SAP v. 3 (Table **16**; P=0.1026). The repeated measures analysis is nominally positive at several timepoints and demonstrated

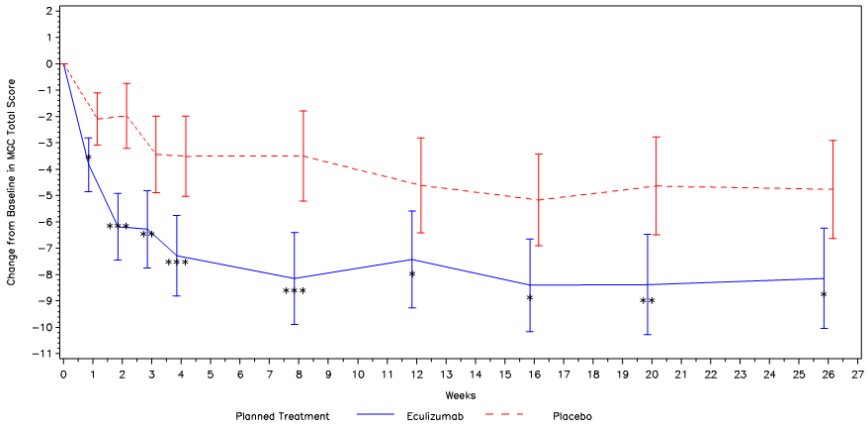
Table 16 Myasthenia Gravis Composite total score Study 301

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)	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		

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Max = maximum; MGC = Myasthenia Gravis Composite score; Min = minimum; SD = standard deviation; SEM = standard error of the mean

Source: Clinical Study Report ECU-MG-301 p. 102/208

Figure 9 Myasthenia Gravis Composite Total Score Repeated Measures Analysis



Source: Clinical Study Report ECU-MG-301 p. 104/208

According to the Statistical review following the SAP v. 2, the MGC showed a significant treatment effect (P = 0.037).

Medical Officer's Comments: Considering that I have adapted the SAP v.2 as the best method for analyzing the data of this study, the significance level determined by the statistical reviewer (P = 0.037) should be considered as the most appropriate result of this analysis. This allows for the MGC to be considered positive and for the testing of the 5th secondary endpoint. However, the MGC scale is primarily made up of items that are part of a routine neurological exam and the results may not reflect a true clinical benefit for the patient.

Secondary Endpoint #5 – Myasthenia Gravis-Quality of Life 15 Item Score

The Myasthenia Gravis-Quality of Life 15 Item Score was significantly positive using the SAP v.2 (Table 17; P=0.0406).

Table 17 Myasthenia Gravis-Quality of Life 15 Item Score as analyzed with the SAP v.2

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)	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		

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Max = maximum; MG-QoL15 = Myasthenia Gravis Quality of Life 15-item scale; Min = minimum; SD = standard deviation; SEM = standard error of the mean

Source: Clinical Study Report ECU-MG-301 p. 106/208

According to the Statistical review following the SAP v. 2, the MGC showed a significant treatment effect (P = 0.0119).

Medical Officer's Comments: Considering that I have adapted the v.2 as the best method for analyzing the data of this study, which means that the 4th endpoint should be considered as positive, consideration of this 5th endpoint is allowable. The MGQoL is statistically positive by both v. 2 and 3 of the SAP. However, several items in this scale (e.g.,) may not specifically measure drug effects, so I would not add this endpoint to labeling.

7.1.3. Analysis by Subpopulation

Covariates derived from datasets containing relevant demographic and baseline factors were explored by performing regression analyses of the change from baseline in a dataset constructed by the review team's biostatistics reviewer that adhered to the v. 2 SAP. Several factors including those seen in Figure 10, including site (SITEID), treatment (TRTA), race (RACE), and baseline immunosuppressive therapy (ISTDAY1). Because an improvement in the MGADL is signified by a negative change, I focused on factors with a "-" estimate from the analysis, although the "+" change for the race factor was followed up to see if there were ethnic differences in response to the drug. I included parameters described in the section of this review

for baseline analyses, as well as the baseline score of the MGADL crossed with each parameter in the model. Only **treatment** was positive when the effect of parameters was evaluated in this model (ANOVA, nominal P = 0.0411) suggesting further exploration of intrinsic and extrinsic factors affecting efficacy did not need to be considered in labeling.

This analysis is similar to that demonstrated in Figure 7 except that here I used linear regression with the change from baseline being continuous and in Figure 7 I used a categorical responder definition with a chi-square analysis.

Figure 10 Regression Analysis of the Change for Baseline for the MGCADL Endpoint (SAP v.2)

Analysis of Generalized Claim

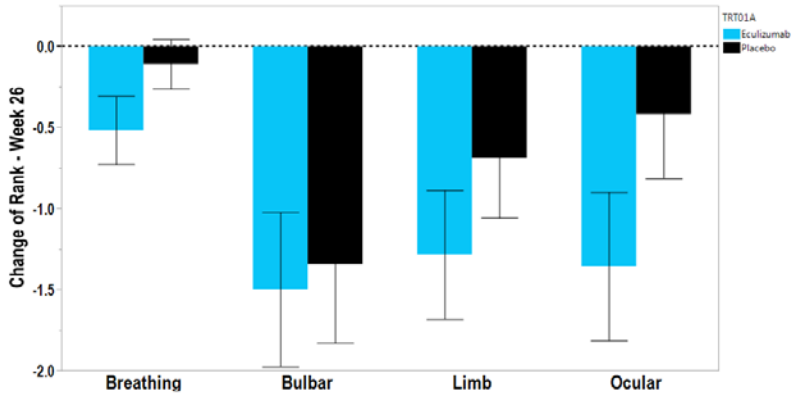
I also analyzed the MG-ADL data to determine if there were unequal responses between the domains of the scale, the ocular, bulbar, breathing, and limb. I did this because the applicant wanted a claim for generalized MG and while there was not an inherent reason to believe the drug would affect different muscle systems uniquely, this analysis would be a systematic approach to verify the claim.

Figure 11 Rank Analysis for Effect of Factors on the MGADL Endpoint

Source	LogWorth	PValue
TRT01A	1.386	0.04107
COUNTRY	1.145	0.07154
SEX	0.991	0.10216
BASE*COUNTRY	0.842	0.14381
MGFACGC	0.801	0.15799
BASE*ISTDAY1	0.770	0.17001
AGEGR1	0.612	0.24418
ETHNIC	0.533	0.29329
ISTDAY1	0.506	0.31210 ^
RACE	0.413	0.38645
MGFAST	0.353	0.44394
BASE*RACE	0.323	0.47541
BASE*TRT01A	0.200	0.63120
BASE*ETHNIC	0.030	0.93369
BASE*SEX	0.025	0.94382
BASE*REGION	.	.
BASE*JAPANDSC	.	.
BASE	.	.
REGION	.	.
JAPANDSC	.	.

Analysis of the change in rank (Figure 11) at week 26 suggests the treatment effect is consistent across domains of the MG-ADL. The analysis dataset was prepared by the review team's biostat group based on SAP v. 2. **I therefore recommend the claim of <u>generalized</u> Myasthenia Gravis.**

Figure 12 Mean Change in Rank of MG-ADL Score (95%CI) by Treatment



Note –Lower mean rank changes represent more favorable clinical status

7.2. **Study Title: ECU-MG-302 A Phase III, Open-Label Extension Trial of ECU-MG-301 to Evaluate the Safety and Efficacy of Eculizumab in Subjects with Refractory Generalized Myasthenia Gravis (gMG)**

7.2.1. **Study Design**

Objectives and Overview (as stated by the sponsor)
Primary Objective:

- To evaluate the long-term safety of eculizumab in patients with refractory generalized Myasthenia Gravis (gMG).

Secondary Objectives:
The secondary objectives of this study are to:

- Evaluate the long-term efficacy of eculizumab in patients with refractory gMG as measured by the improvement or maintenance of the MG-specific Activities of Daily Living (MG-ADL) total score.
- Evaluate the long-term efficacy of eculizumab by additional efficacy measures, including:
  − Quantitative Myasthenia Gravis (QMG) score
  − Myasthenia Gravis Composite (MGC) score
  − Improvement or maintenance in primary symptoms that were most clinically meaningful to the patient
- Characterize the effect of eculizumab on quality of life measures
- Describe the pharmacokinetics (PK) and pharmacodynamics (PD) of eculizumab in patients with refractory gMG.

Study Design
This is an open-label, multi-center study. Patients were to enter Study ECU-MG-302 within 2 weeks after completing their Week 26 visit in Study ECU-MG-301. There are 3 phases in Study ECU-MG-302:

- A 4-week Blind Induction Phase that was specifically designed to maintain each patient's blinded treatment assignment in Study ECU-MG-301,

- An Open-Label Maintenance Phase, and
- A Safety Follow-up Period for patients who withdrew from the study or discontinued eculizumab treatment at any time and for any reason after receiving any amount of eculizumab.

Population

114 patients enrolled and received at least 1 dose of study drug as part of Study ECU-MG-302. One patient was excluded from this interim analysis, because the Sweden Health Authority did not approve the protocol amendment that allowed for the interim analysis; thus, 113 total patients are included in this interim analysis.

Key inclusion and exclusion criteria

- Inclusion – completed study 301
- Exclusion
  - Withdrew from Study 302 because of an adverse event related to study drug
  - Had an unresolved meningococcal infection

Treatment

- Blinded induction phase - All patients received blinded study drug weekly for 4 weeks
  - Patients who had received eculizumab in Study ECU-MG-301 were administered eculizumab (4 vials/1200 mg) on Day 1 and Week 2 (Visits 1 and 3), and placebo (4 vials/0 mg) at Weeks 1 and 3 (Visits 2 and 4).
  - Patients who had received placebo in Study ECU-MG-301 were administered eculizumab/placebo (3 vials/900 mg, plus 1 vial/0 mg, respectively) on Day 1 and Weeks 1 through 3 (Visits 1 through 4).
- Open label maintenance phase - Patients received open-label eculizumab (4 vials/1200 mg) every 2 weeks (14 ± 2 days) starting at Visit 5 (Week 4) and continued throughout the study.

The duration of the study for an individual patient is dependent on when the patient entered the study; the maximum duration has been 4 years for any patient.

Assessments

Primary - Change from Baseline in the MG-ADL total score.

Secondary endpoints

- Change from Baseline in QMG total score
- Proportion of patients with at least a 3-point reduction in the MG-ADL total score from Baseline and with no rescue therapy
- Proportion of patients with at least a 5-point reduction in the QMG total score from Baseline and with no rescue therapy
- Change from Baseline in the MGC total score
- Change from Baseline in Myasthenia Gravis Quality of Life 15-item scale (MG-QoL15)

Tertiary (exploratory)

- Time to response as measured by the reduction in the MG-ADL total score (3-point reduction from Baseline)
- Change from Baseline in Quality of Life in Neurological Disorders (Neuro-QoL) Fatigue
- Change from Baseline in European Quality of Life Health 5-item questionnaire (EQ-5D)
- Change from Baseline in the MG-ADL individual items and subcategories for the bulbar (Items 1, 2, and 3), respiratory (Item 4), limb (Items 5 and 6), and ocular (Items 7 and 8) in patients with abnormal baseline scores for the particular item or subcategory
- Myasthenia Gravis Foundation of America Post-Interventional Status [MGFA-PIS] and
- Incidence of clinical deterioration

Analyses
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.

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.

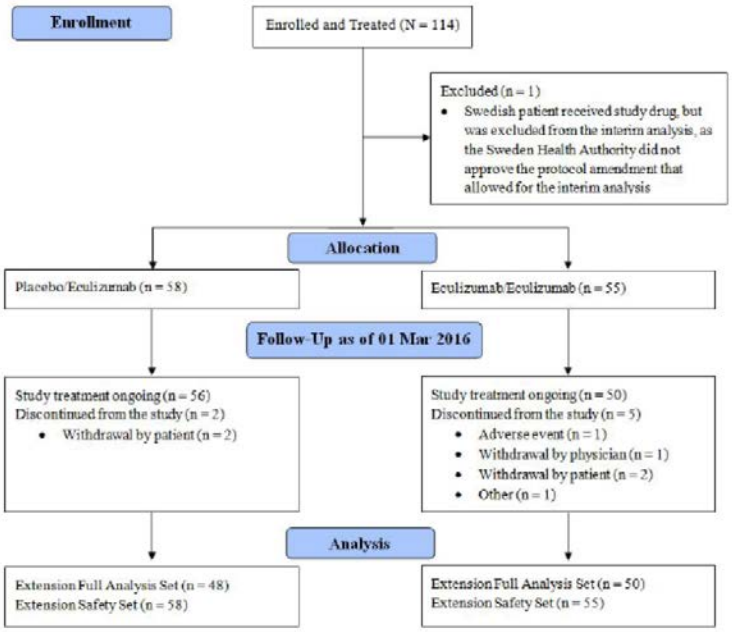
Analyses did not include adjustments made for multiple comparisons and endpoints. Missing primary endpoint assessments were not imputed. A primary endpoint was declared (The primary efficacy endpoint was the change from Baseline in the MG-ADL total score.), however, there is no designation of a particular point in time for the primary in this open label extension**. I therefore assert that all P values from secondary endpoints of this study be considered as nominal**.[5]

7.2.2. **Study 302 Results**

Disposition

[5] Per the Interim CSR Section 11.4.3.5 p.101/140 and the SAP

Figure 13 Disposition of Patients in Study 302



Source: Interim Clinical Study Report ECU-MG-302 (Clinical Study Database Cutoff: 01 Mar 2016), p 69/140

As of 01 Mar 2016, 17 patients in the eculizumab/eculizumab arm had been treated for ≥26 weeks in Study ECU-MG-302, of whom 6 had been treated for ≥52 weeks; 20 patients in the Placebo / eculizumab arm had been treated for ≥26 weeks in Study ECU-MG-302, of whom 9 had been treated for ≥52 weeks

Medical Officer's Comments: These data are relatively incomplete in terms of subjects that finished (several are still in the study because of the cutoff date) but the numbers dropping out is *relatively* small so the data seems interpretable.

Protocol Deviations
Protocol deviations were reviewed by this Medical Reviewer and were not felt to affect the interpretation of this study.

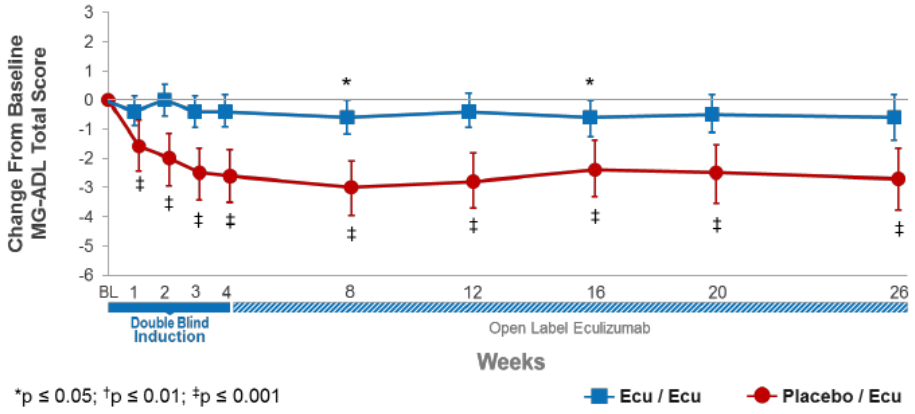
Efficacy/Pharmacodynamics

Primary Endpoint – MG-ADL

The treatment effect observed during Study ECU-MG-301 in patients treated with eculizumab during that study (-4.6 [-5.9, -3.3]) was sustained in Study ECU-MG-302 with a mean (95% CI) change in MG-ADL total score from ECU-MG-301 Baseline at Weeks 1, 8, and 26 of Study ECU-MG-302 of -5.1 (-6.4, -3.9), -5.0 (-6.4, -3.7), and -4.6 (-6.4, -2.8), respectively.

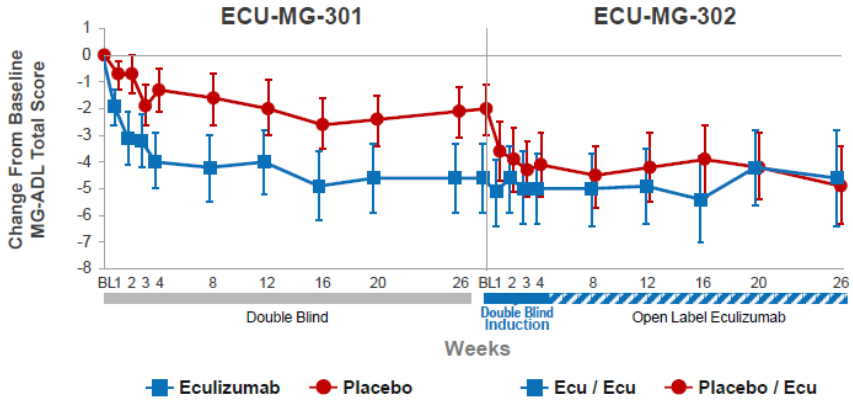
In the placebo/eculizumab arm, a change from ECU-MG-302 Baseline in MG-ADL total score was observed as early as Week 1 (-1.6 [-2.44, -0.69]; nominal $p = 0.0007$). The majority of the overall treatment effect was achieved by Week 3 (-2.5 [-3.44, -1.65]; nominal $p<0.0001$).

Figure 14 Change from Baseline in the MG-ADL Total Score by Treatment Arm over Time from Baseline of Study 302



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 14).

Figure 15 Change from Baseline in the MG-ADL Total Score by Treatment Arm over Time from Baseline of Study 301



Note: 95% CI is based on t-distribution for each treatment arm at each visit.

Medical Officer's Comments: As the SAP for Study 302 describes summarizing these results at each visit and does not provide a statistical model, significance level, or approach to Type I error control for this analysis, I think the primary endpoint significance is nominal only.

Secondary Endpoints

Medical Officer's Comments: Since the applicant did not correct for multiplicity, the inferential analyses yield only nominal results and should not be considered as statistically

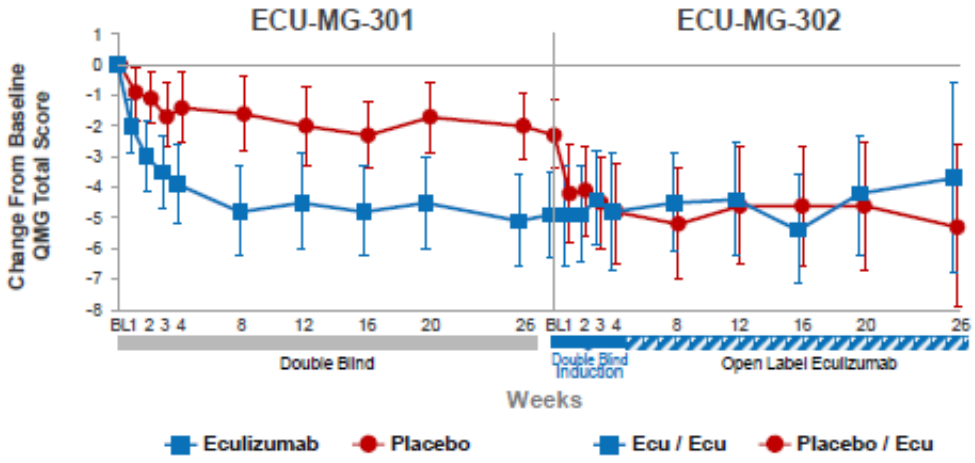
positive, only nominal. Nonetheless, they generally support the finding of the primary in this study and the Contribution of this study to support Study 301.

Secondary Endpoint – QMG

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 from ECU-MG-302 Baseline in QMG total score was observed at Week 1 (-1.8 [-2.96, -0.70]; nominal p = 0.0019). The majority of the overall treatment effect was achieved by Week 4 (-3.0 [-4.18, -1.85]; nominal p<0.0001) during the Blind Induction Phase, and was sustained through Week 26 (-3.1 [-4.42, -1.71]; nominal p<0.0001) (Figure 15).

Figure 16 Change from Baseline in the change in QMG total score by Treatment Arm over Time from Baseline of Study 301



The proportion of patients with a ≥3-point reduction in MG-ADL total score

The eculizumab/eculizumab arm exhibited a -3-point responder rate of 56.3% (9 of 16 patients) at Week 26 of Study ECU-MG-302; this responder rate is similar to that seen at Week 26 of Study ECU-MG-301 (60.0% [30 of 50 patients]).

At Week 26 of Study ECU-MG-301, 18 (37.5%) patients in the placebo/eculizumab arm had attained a ≥3-point improvement in MG-ADL total score and no rescue therapy. At Week 4 of Study ECU-MG-302, 33 of 42 (78.6%) placebo/eculizumab patients obtained a ≥3-point improvement in MG-ADL total score with no rescue therapy. Fifteen (15) of 20 (75.0%) placebo / eculizumab patients obtained a ≥3-point improvement in MG-ADL total score with no rescue therapy over 26 weeks of treatment with eculizumab.

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

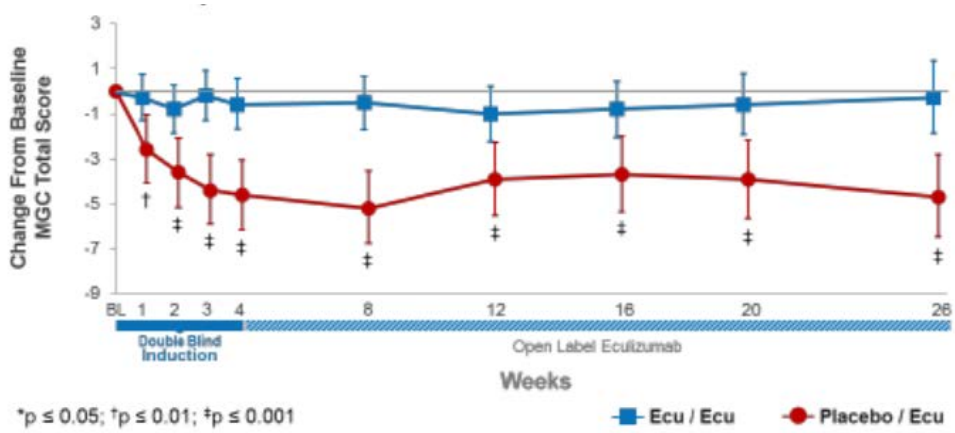
The eculizumab/eculizumab arm exhibited a responder rate of 43.8% (7 of 16 patients) at Week 26 of Study ECU-MG-302; this responder rate is similar to that seen at Week 26 of Study ECU-MG-301 (51.0% [25 of 49 patients]).

At Week 26 of Study ECU-MG-301, 10 (20.8%) patients in the placebo/eculizumab arm had attained a ≥5-point improvement in QMG total score and no rescue therapy. 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. Ten (10) of 20 (50.0%) placebo/eculizumab patients obtained a ≥5-point improvement in QMG total score with no rescue therapy over 26 weeks of treatment with eculizumab.

Myasthenia Gravis Composite Total Score Change from ECU-MG-302 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]) seemed 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 (Figure 16).

Figure 17 Change from Baseline in the change in MGC total score by Treatment Arm over Time from Baseline of Study 302

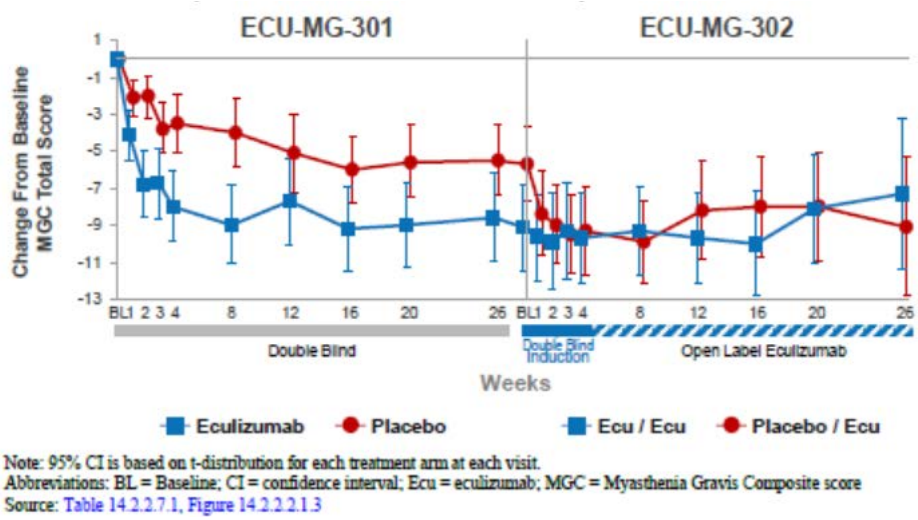


Note: The LS mean and 95% CI are based on a Repeated-Measures model of change from ECU-MG-302 Baseline in MGC total score for the treatment arms of placebo/eculizumab and eculizumab/eculizumab separately. Each Repeated-Measures model included the following terms: visit and MGC total score at Baseline. Missing values were not imputed. Nominal p-values are for the statistical significance testing of the mean change from ECU-MG-302 Baseline in MGC total score by visit using a Repeated-Measures model for each arm.
Abbreviations: BL = Baseline; CI = confidence interval; Ecu = eculizumab; LS = least squares; MGC = Myasthenia Gravis Composite score
Source: Table 14.2.2.17.1, Table 14.2.2.18.1, Figure 14.2.2.4.1.2

In the placebo/eculizumab arm, a change (mean [95% CI]) from ECU-MG-301 Baseline in MGC total score was observed at Week 1 of -8.4 [-10.6, -6.1]) in 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 appeared sustained through Week 26 (-9.1 [-12.8, -5.3]) (Figure 17).

Figure 18 Change from Baseline in the MGC Total Score by Treatment Arm over Time from Baseline of Study 301



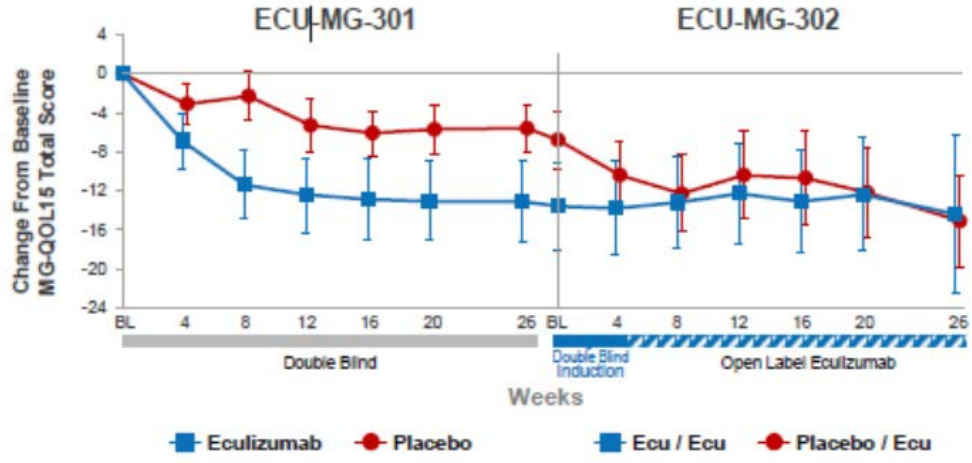
Note: 95% CI is based on t-distribution for each treatment arm at each visit.
Abbreviations: BL = Baseline; CI = confidence interval; Ecu = eculizumab; MGC = Myasthenia Gravis Composite score
Source: Table 14.2.2.7.1, Figure 14.2.2.2.1.3

Myasthenia Gravis Quality of Life 15 Total Score Change from ECU-MG-302 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]) seems to be 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]) (Figure 18). 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 18).

Figure 19 Change from Baseline in the MG-QoL15 Total Score by Treatment Arm over Time from Baseline of Study 301

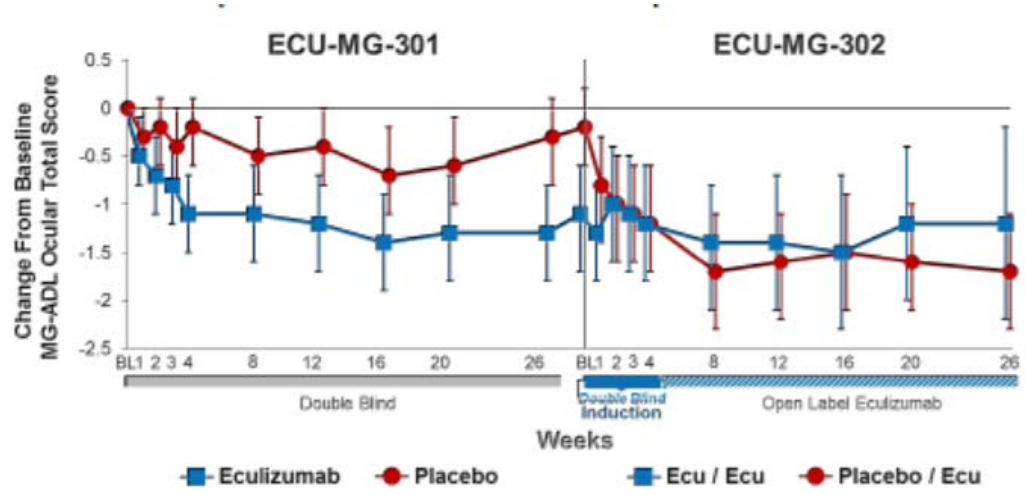


Note: 95% CI is based on t-distribution for each treatment arm at each visit.
Abbreviations: BL = Baseline; CI = confidence interval; Ecu = eculizumab; MG-QoL15 = Myasthenia Gravis Quality of Life 15-item scale
Source: Table 14.2.2.11.1, Figure 14.2.2.3.1.3

MG-ADL Ocular (Items 7 and 8) Scores

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: -1.3 [-1.8, -0.8]) appears to be sustained in Study ECU-MG-302 (eculizumab/eculizumab arm), with a mean (95% CI) change in MG-ADL ocular score from ECU-MG-301 Baseline at Weeks 1, 8, and 26 of Study ECU-MG-302 of -1.3 (-1.8, -0.8), -1.4 (-2.1, -0.8), and -1.2 (-2.2, -0.2), respectively. In the placebo/eculizumab arm, a change (mean [95% CI]) from ECU-MG-301 Baseline in MG-ADL ocular score was observed as early as Week 1 (-0.8 [-1.4, -0.3]) of Study ECU-MG-302. The majority of the overall treatment effect was achieved by Week 8 (-1.7 [-2.3, -1.1]), and was sustained through Week 26 (-1.7 [-2.3, -1.1]) (Figure 19).

Figure 20 Change from Baseline in the MG-ADL Ocular Score by Treatment Arm over Time



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
Source: Table 14.2.3.24.1

Change from Baseline in the Myasthenia Gravis Foundation of America Post-intervention Status by Treatment Arm over Time from Baseline of Study 301

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 still on study) 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% patients still on study) 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 (Table 18).

Table 18 Change from Baseline in the MGFA Post-Intervention Status by Treatment Arm over Time from Baseline of Study 301

Visit	Change from ECU-MG-301 Baseline in MGFA Post-Intervention Status					
	Placebo/Eculizumab (N = 48)			Eculizumab/Eculizumab (N = 50)		
	Improved n/N (%)	Unchanged n/N (%)	Worse n/N (%)	Improved n/N (%)	Unchanged n/N (%)	Worse n/N (%)
ECU-MG-301 Week 4	11/48 (22.9)	34/48 (70.8)	3/48 (6.3)	29/49 (59.2)	20/49 (40.8)	0/49 (0.0)
ECU-MG-301 Week 12	18/48 (37.5)	27/48 (56.3)	3/48 (6.3)	28/48 (58.3)	19/48 (39.6)	1/48 (2.1)
ECU-MG-301 Week 26	20/48 (41.7)	25/48 (52.1)	3/48 (6.3)	31/50 (62.0)	18/50 (36.0)	1/50 (2.0)
ECU-MG-302 Week 26	17/20 (85.0)	3/20 (15.0)	0/20 (0.0)	14/15 (93.3)	1/15 (6.7)	0/15 (0.0)
ECU-MG-302 Week 40	14/16 (87.5)	2/16 (12.5)	0/16 (0.0)	8/12 (66.7)	3/12 (25.0)	1/12 (8.3)
ECU-MG-302 Week 52	8/9 (88.9)	1/9 (11.1)	0/9 (0.0)	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)

Abbreviations: MGFA = Myasthenia Gravis Foundation of America
Source: Table 14.2.3.5.1

Clinical Deterioration

A total of 13 (11.5%) patients overall experienced 20 clinical deterioration events (Table 19); 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 Section 9.5.1.1.7; 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 (Table 19).

Table 19 Summary of Patients Reporting Clinical Deterioration and Use of Rescue Therapy during the Study Period by Treatment Arm

Variable	Statistic	Placebo/ Eculizumab (N = 58)	Eculizumab/ Eculizumab (N = 55)	Total (N = 113)
Total Number of Patients Reporting Clinical Deterioration	n (%)	5 (8.6)	8 (14.5)	13 (11.5)
Total Number of Patients Reporting Clinical Deterioration Based on Protocol Criteria	n (%)	4 (6.9)	7 (12.7)	11 (9.7)
Total Number of Patients Experiencing the Following Events				
MG Crisis	n (%)	0 (0.0)	1 (1.8)	1 (0.9)
Total Number of Clinical Deterioration Events	n	6	14	20
MG Crisis	n	0	1	1
Total Number of Patients Requiring Rescue Therapy	n (%)	5 (8.6)	8 (14.5)	13 (11.5)
Total Number of Clinical Deterioration Events Requiring Rescue Therapy	n	6	14	20

Abbreviations: MG = myasthenia gravis
Source: Table 14.2.4.1.3

7.3. **Study Title:** C08-001 A Randomized, Double-Blind, Placebo-Controlled, Cross-Over, Multi-Center Study of Eculizumab in Patients with Generalized Myasthenia Gravis (gMG) who have Moderate to Severe Muscle Weakness Despite Treatment with Immunosuppressants

7.3.1. **Study Design**

Objectives

Primary Objective

- Safety: Evaluation of treatment-emergent adverse events (TEAEs)
- Efficacy: The percentage of patients with a 3-point reduction from baseline in the Quantitative Myasthenia Gravis (QMG) total score for disease severity at the end of each treatment period

Secondary Objectives

Evaluation of change from baseline in

- QMG total score for disease severity,
- the two most affected QMG individual test items,
- the Myasthenia Gravis Foundation of America (MGFA) Post-Intervention Status (PIS),
- MG Activities of Daily Living profile (MG-ADL),
- respiratory function tests including spirometry to characterize the degree of involvement of respiratory muscles, and
- Quality of Life (QoL) instrument SF- 36.

Exploratory Objectives

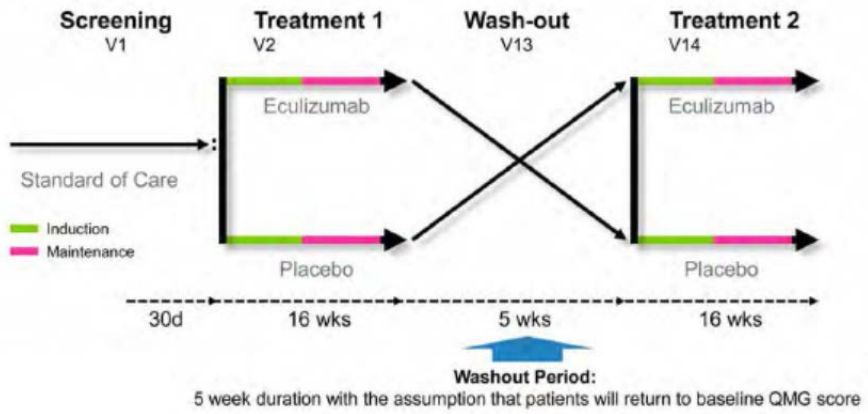
Evaluation of the following:

- change from baseline in single fiber electromyography (SFEMG),
- change from baseline in Myasthenia Gravis Quality of Life (MG-QOL15),
- MGFA Morbidity and Mortality, and
- Change from baseline in binding anti-acetylcholine receptor (AChR) antibody (Ab) titer.

Design

This was a randomized, double-blind, placebo-controlled, cross-over, multicenter study. Patients received either eculizumab or placebo in Treatment Period 1 for 16 weeks. At the end of 16 weeks, patients entered the Wash-Out period of 35 days. Patients then entered Treatment Period 2 (the cross-over Treatment Period) to receive the alternative treatment for 16 weeks.

Figure 21 Study Design of C08-001



Population

A total of 14 patients were treated and analyzed. Due to slow recruitment during 2.25 years, the study was closed to enrollment prior to reaching the planned 24 patients. All 14 patients who were treated with either eculizumab and/or placebo were included in the safety population. A total of 12 patients who received any amount of study drug in both treatment periods were included in the intent-to-treat (ITT) population.

Key Inclusion and Exclusion Criteria
1. Male or female patient ≥18 to ≤80 years old.
2. Generalized MG with prominent clinical symptoms.
3. Diagnosis of MG using the following tests:
- A positive serologic test for binding anti-AChR Abs at screening,

and
- One of the following:

a) History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation, or
b) History of positive anticholinesterase test, e.g. edrophonium chloride test, or
c) Patient has demonstrated improvement in MG signs on oral acetylcholinesterase inhibitors (AChEI) as assessed by treating physician.
4. MGFA Clinical Classification Class II, III or IVa.
5. QMG for Disease Severity total score ≥12.
6. Minimum score of 2, in four or more test items in the QMG.
7. Patients must have failed treatment or failed to achieve significant clinical benefit with at least two immunomodulators, i.e. corticosteroids, azathioprine (AZA), cyclosporine, tacrolimus (Prograf®), mycophenolic acid, cyclophosphamide, methotrexate (MTX), or intravenous immunoglobulin (IVIG) after one year of treatment.
8. Patients who entered the study taking AZA must have been on AZA for ≥12 months and on a stable dose for ≥2 months prior to screening. The dose level was not to be changed during the study.

9. Patients who entered the study taking other immunosuppressive treatments, e.g. MTX, cyclosporine, tacrolimus (Prograf®), mycophenolic acid, or cyclophosphamide, must have been on treatment for ≥6 months and on a stable dose for ≥2 months prior to screening. The dose level was not to be changed during the study.
10. Patients who entered the study taking oral corticosteroids must have been on a stable dose for ≥ 4 weeks (28 days) prior to screening, and the dose level was to remain stable during the study. If a decrease in steroids was considered based on clinical evaluation, sponsor approval was to be obtained prior to the change in dose in order for the patient to remain on study. If the dose level was increased above the dose level reported at Visit 1, the patient was to be deemed a treatment failure and was to be discontinued from the study.
11. Patients who entered the study taking an AChEI must have been on a stable dose for ≥2 weeks prior to screening. The dose level was not to be changed during the study with the exception that the dose was to be held for at least 12 hours prior to QMG and SFEMG testing. If a decrease in the AChEI was considered, based on clinical evaluation, sponsor approval was to be obtained prior to the change in dose in order for the patient to remain on study.

Exclusion
1. History of thymoma or other neoplasms of the thymus.
2. History of thymectomy within 12 months prior to screening.
3. MG status, which in the opinion of the Investigator, was unstable or with fixed weakness (i.e. "burned-out") such that the patient was unlikely to respond to therapy based on the patient's disease severity, pace of progression and prior MG treatment history.
6. Current chronic use of plasmapheresis/plasma exchange defined as requiring plasma exchange on a regular basis for the management of muscle weakness two or more times in one year, or any plasma exchange within 3 months prior to screening.
7. IVIG treatment within 8 weeks prior to screening.
8. Use of etanercept [tumor necrosis factor (TNF) inhibitor] within 2 months prior to screening.
9. Use of rituximab within 6 months prior to screening.
10. Severe weakness predominantly affecting oropharyngeal or respiratory muscles or both (MGFA Clinical Classification IVb).
11. Crisis or impending crisis as evidenced by forced vital capacity (FVC) <10 milliliter (ml)/kilogram (kg) or <35%.
12. Weakness only affecting ocular or peri-ocular muscles (MGFA Clinical Classification I).
14. History of splenectomy.
15. Participation in any other investigational drug study or exposure to other investigational agent, device, or procedures within 30 days prior to screening.
16. History of meningococcal disease.
17. Known or suspected complement deficiency.
18. Patients who were not vaccinated against *N. meningitidis* at least 14 days prior to Visit 2.

Treatment

Test Product: Induction Period: Patients received either eculizumab 600 mg or matching placebo via intravenous (IV) infusion once a week (every 7 ± 2 days) for 4 weeks followed by eculizumab 900 mg or matching placebo for the fifth dose 7 ± 2 days later.

Maintenance Period: Patients received either eculizumab 900 mg or matching placebo via IV infusion every 2 weeks (every 14 ± 2 days) for 6 doses.

Reference: placebo contained the same buffer components as the eculizumab vials but without active ingredient.

Duration of Treatment: The planned duration of treatment was 32 weeks (16 weeks for each treatment period) with a 5 week wash-out period in between.

Concomitant Therapies

- Azathioprine. The patient must have been taking AZA for ≥12 months and on a stable dose for ≥2 months, prior to the study Screening Visit. The dose level of AZA was not to be changed during the study.
- Methotrexate. The patient must have been taking MTX for ≥6 months and on a stable dose for ≥2 months, prior to the study Screening Visit. The dose level of MTX was not to be changed during the study.
- Cyclosporine. The patient must have been taking cyclosporine for ≥6 months and on a stable dose for ≥2 months, prior to the study Screening Visit. The dose level of cyclosporine was not to be changed during the study.
- Tacrolimus (Prograf®). The patient must have been taking tacrolimus for ≥6 months and on a stable dose for ≥2 months, prior to the study Screening Visit. The dose level was not to be changed during the study.
- Mycophenolic. The patient must have been taking Cellcept or Myfortic for ≥6 months and on a stable dose for ≥2 months, prior to the study Screening Visit. The dose level was not to be changed during the study.
- Cyclophosphamide. The patient must have been taking cyclophosphamide for ≥6 months and on a stable dose for ≥2 months, prior to the study Screening Visit. The dose level was not to be changed during the study.
- Corticosteroids. The patient must have been taking a stable dose for ≥4 weeks prior to the study Screening Visit and was to be kept stable throughout the study. However, if at any time during the study a decrease in the steroid dose below the baseline dose level reported at Screening Visit 1 was contemplated (based on clinical evaluation), sponsor approval was to be obtained prior to the dose reduction, in order for the patient to remain on study. Additionally, if at any time during the study an increase in the dose above the baseline dose level reported at Screening Visit 1 was required, the patient would be deemed a treatment failure and discontinued from the study.
- Acetylcholinesterase inhibitor. The patient must have been taking a stable dose for ≥2 weeks prior to the study Screening Visit and was to be kept stable throughout the study with the exception that the dose was to be held for at least 12 hours prior to scheduled QMG and SFEMG testing of the patient. Additionally, if a decrease in the dose of AChEI was required (based on clinical evaluation), sponsor approval was to be obtained prior to the dose reduction, in order for the patient to remain on study.
- Blood transfusion. When required during the study, a patient could receive a blood transfusion according the study site's standard procedures (administration with packed

red blood cells (RBCs) in an optimal additive solution was recommended; transfusion with whole blood containing complement was to be avoided).

The following medications or therapies were not to be given during the study; if any of the following had to be given, the patient was to be deemed a treatment failure and discontinued from the study:

- Rituximab
- Plasmapheresis/plasma exchange

Assessments

Efficacy:

Primary endpoint

- The primary efficacy endpoint was the percentage of patients with a 3-point reduction from baseline in the QMG total score for disease severity at the end of each treatment period.

Secondary endpoints

The secondary endpoints were change from baseline to the end of each treatment period:

- QMG total score for disease severity;
- Two most affected QMG individual test items;
- MGFA PIS;
- MG-ADL;
- Respiratory function tests including spirometry to characterize the degree of involvement of respiratory muscles;
- QoL instrument SF-36.

Exploratory endpoints

The exploratory endpoints were change from baseline to the end of each treatment period:

- SFEMG;
- MG-QOL15;
- MGFA Morbidity and Mortality;
- Binding anti-AChR Ab titer.

Safety:

The primary safety endpoint was the assessment of TEAEs. Vital signs (VS), clinical laboratory and electrocardiography (ECG) data were also analyzed.

Pharmacokinetic (PK), Pharmacodynamic (PD) and immunogenicity:

- Assessment of the pharmacokinetics (PK) of eculizumab, trough and peak concentrations during the induction and maintenance treatment phase. Clearance and terminal half-life of eculizumab were estimated.
- Assessment pharmacodynamics (PD) of eculizumab for serum hemolytic activity and therefore C5 complement activity inhibition.

Analysis Plan

Adjustments for multiple comparisons and multiplicity were not performed.

7.3.2. Study Results

7.3.3. Disposition

Table 20 presents the disposition of the CN08-001 trial up to the point the PI terminated it for lack of enrollment. Four subjects discontinued. Patient (b) (6) discontinued during the Screening Visit, prior to randomization, due to an SAE; technically this was not a discontinuation as the Safety Population was defined as all patients who received any amount of investigational product. Patient (b) (6) discontinued the study because of need for plasma exchange therapy for MG crisis while on placebo treatment, which the physician described as lack of efficacy. Two subjects were discontinued when the trial was terminated.

Table 20 Disposition of Patients in Trial CN08-001

Disposition	Patients (N=15) N (%)
Met screening eligibility requirements	15 (100)
Treated	
Treatment Period 1 (Safety Population)	14 (93)
Treatment Period 2 (Intent-to-Treat Population)	12 (80)
Status	
Completed the study	11 (73)
Discontinued from study	4 (27)
Reason for discontinuation	
Serious adverse event	1 (7)
Lack of efficacy	1 (7)
Other reason: Sponsor ended study early	2 (13)

Source: Table 14.1.1, Listing 16.2.1.1, Listing 16.2.5.2

Demographics
The numbers of patients in this study were quite small, However, from my analyses, I noted that the treatment sequences were generally balance with respect to Age, Sex, Country, and Race. All but one subject was on AchEI and 10/14 patients were on ISTs.

Efficacy Assessments

Medical Officer's Comments: This study showed a carryover effect between crossover periods so only period one results are evaluated. Since this was not prespecified, the resulting inferential statistics are only considered as nominal. While several of the following endpoints are nominally positive or demonstrate a trend, interpretation of this study is difficult because of the change in analysis and the limited number of subjects.

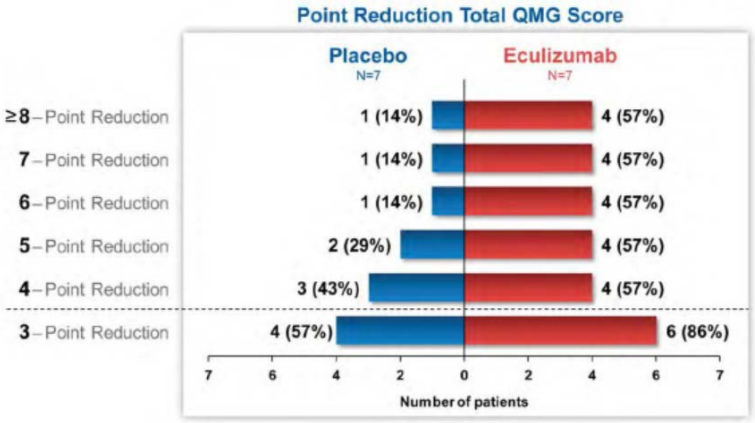
Primary endpoint - Percentage of Patients with a 3-Point Reduction from Baseline in the Quantitative Myasthenia Gravis Total Score for Disease Severity

The QMG Total Score for patients in the Eculizumab to Placebo randomization treatment sequence did not return to their Treatment Period 1 baseline scores at the beginning of Treatment Period 2 after the 35-day Washout Period, suggesting the presence of an eculizumab treatment carry-over effect. Due to this carry-over effect, results for the primary efficacy endpoint and key secondary efficacy endpoints (change from baseline in QMG total score and MG-ADL) were analyzed for Treatment Period 1, and efficacy data for Treatment Period 2 are presented in descriptive terms only.

A 3-point reduction in QMG scores was noted within the first 3 weeks of treatment with a median response time for the 7 patients treated with eculizumab in Treatment Period 1 of 12 days (range 7-21 days). The median duration of a sustained 3-point change was 92 days. Eighty-six percent (6/7) of the eculizumab-treated patients achieved the primary endpoint of at least a 3-point reduction from baseline in QMG total scores compared to only 57% (4/7) of placebo-treated patients at the end of Treatment Period 1. 57% of patients (4/7) treated with eculizumab obtained at least an 8-point reduction in the total QMG score as compared to only 14% (1/7) of patients receiving placebo.

Of the 6 patients treated with eculizumab in Treatment Period 2, four patients (b) (6), (b) (6), (b) (6) and (b) (6)) had changes in QMG scores of 6 points or greater: -6, -6, -10 and -12.

Figure 22 Proportion of Subjects by Change in the QMG Score by Treatment



Secondary Endpoints

- Change from Baseline in the QMG Total Score for Disease Severity

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; nominal p=0.014). The change in mean QMG total score from baseline to last visit in Treatment Period 1 demonstrated a trend towards significance between eculizumab -7.43 versus placebo -2.71; (ANOVA nominal p=0.058 with baseline QMG as a covariate and effects for treatment period and sequence).

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

Change in the MGFA PIS categories (improved, unchanged, worse, exacerbation, and died of MG) were evaluated. Although it was recommended by the MGFA to use a pre-defined increase / decrease in a quantitative measure, such as QMG score, to define the criteria for "Improved" and "Worsening", no pre-defined criteria was set for this protocol. MGFA PIS was determined by the Investigators based on their clinical evaluation.

- No eculizumab-treated patients worsened or had MG exacerbation. Overall MGFA PIS for 84.6% (11/13) patients was Improved and for 15.4% (2/13) patients was Unchanged on the last visit in their eculizumab treatment, versus 61.5% (8/13) patients Improved and 5/13 (38.5%) Unchanged on the last visit in their placebo treatment.

- In Treatment 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.

- In Treatment Period 2, MGFA PIS for 100% (6/6) patients was Improved with eculizumab treatment versus 33.3% (2/6) patients Improved and 67.7% (4/6) Unchanged with placebo treatment. Two patients on placebo showed Worsening at some visits.

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

At the end of Treatment Period 1, there was a nominally significant difference in the MG-ADL score between the eculizumab and placebo, 4.29 (1.8 SD) versus 7.86 (3.7 SD); nominal p=0.041. Additionally, 86% (6/7) of eculizumab treated patients had at least a 3-point change from baseline (considered to be clinically meaningful as noted above) in comparison to only 57% (4/7) placebo-treated patients. Eculizumab patients had a 4-point improvement in mean MG-ADL (-4.14 SD=3.12) compared with placebo patients (-1.43 SD=3.10).

- Change from Baseline in Respiratory Function Tests, including Spirometry, to Characterize the Degree of Involvement of Respiratory Muscles

No treatment differences were noted in the NIF or FVC, although the numbers of subjects may have been too low or duration of testing too short to detect any differences.

- Change from Baseline in the Quality of Life Instrument SF-36

- For the combined 13 patients from Treatment Period 1 and Treatment Period 2 who were treated with eculizumab, the mean Physical Component Score (PCS) improved by almost 9 points (31.8 to 40.6). In contrast, for the combined 13 patients from Treatment Period 1 and Treatment Period 2 who were treated with placebo, the PCS improved by approximately 2 points (38.0 to 40.9).

The improvement in the PCS while on eculizumab appeared driven by a 4.5, 9.7, and 8.8 point improvements in the Bodily Pain, General Health, and Role Physical subscores, respectively. Small changes were seen in the mean Mental Component Score (MCS) between the beginning and end of treatment with both eculizumab or Placebo. The mean Vitality subscore increased by 5.7 points when patients were treated with eculizumab and decreased by 4.3 when patients were treated with Placebo.

Table 21 Change from Baseline in the Quality of Life Instrument SF-36

Component Score/Health Domain	Eculizumab (N=13) SF-36 Score [Mean (SD)]		Placebo (N=13) SF-36 Score [Mean (SD)]	
	Beginning of Period	End of Period	Beginning of Period	End of Period
Physical Component Score	**31.8 (9.64)**	**40.6 (8.73)**	**38.0 (10.59)**	**40.9 (10.52)**
Bodily Pain	47.0 (9.31)	47.2 (9.60)	48.1 (10.31)	50.6 (9.09)
General Health	32.7 (5.46)	37.2 (7.53)	36.4 (10.42)	35.9 (10.63)
Physical Function	28.9 (11.98)	38.6 (11.17)	34.4 (12.86)	38.9 (12.76)
Role Physical	32.4 (11.70)	41.2 (13.17)	39.0 (13.16)	41.2 (13.05)
Mental Component Score	**47.9 (12.91)**	**44.9 (12.77)**	**47.2 (14.20)**	**46.9 (13.66)**
Mental Health	49.4 (9.70)	45.9 (11.47)	47.6 (11.72)	45.0 (14.18)
Role Emotional	38.2 (16.92)	40.9 (16.17)	39.7 (19.30)	44.8 (15.78)
Social Function	42.6 (12.70)	41.3 (10.64)	40.9 (13.99)	45.9 (11.35)
Vitality	40.1 (12.67)	45.8 (10.82)	49.4 (10.65)	45.1 (10.13)

Norm-based scoring involving a linear T-score transformation method was used so that scores for each of the health domain scales and component summary measures have a mean of 50 and a standard deviation of 10 based on the 1998 US general population. Thus, scores above and below 50 are above and below the average, respectively, in the 1998 US general population.

8 Integrated Review of Effectiveness

8.1. Assessment of Efficacy across Trials

From my review I consider that the applicant has met the standard of substantial evidence needed for consideration for approval. I believe this consists of one positive clinical study with confirmatory evidence from the following sources:

- Study 302
- Period 1 of Study C08-001

8.2. **Integrated Assessment of Effectiveness**

Body of Substantial Evidence

Study 301 was an adequate and well controlled trial that was statistically positive on its primary endpoint. I will not revisit issues with the analysis of the primary endpoint here, but I believe the SAP v.2 is the most reasonable approach to analysis of the data and so only those results will be

considered. The 301 study has several attributes one expects from the single study approval scenario including:

- Large multicenter study

Study 301 was greater (most of the cases were half as big) than all but one (that was still enrolling patients) of the completed or enrolling trials I noted in Clintrials.gov (b) (4) . The population in 301 would be considered as refractory, which would have made their enrollment more challenging than most of the trials listed.

- Consistency across study subsets

Regression analysis suggested that there were no factors with significant inhomogeneity between treatment groups (c.f. Section 7.1.3 – Analysis by Subpopulation)

- Multiple studies in a single study

The 302 study could be considered a substudy of 301 since subjects had to complete the latter and would be filtered for tolerability, so I did not consider it an independent substantiation of the results of 301. I describe this study in the context of *supportive* evidence below.

- Multiple endpoints involving different events

All of the secondary endpoints in the hierarchical testing proposed were positive, though the responder analysis cannot be considered an event different from the primary endpoint.

- Statistically very persuasive finding

Sensitivity analyses of the primary endpoint were all positive; this argument is not based on the magnitude of the p value.

- With respect to *supportive* evidence,
  - Discussion of the 302 and CN08-001 studies as supportive evidence

As the SAP for Study 302 describes summarizing these results at each visit and does not provide a statistical model, significance level, or approach to Type I error control for this analysis, I think the primary endpoint significance is nominal only. It would be dicey to consider this statistically significant without caveat. Secondary endpoints were generally supportive however; a plan to control for inflation of alpha was not employed for these, so their analysis can be considered nominal at best (as well as the consideration that the primary cannot truly be tested for significance). Similarly, the CN08-001 study was supportive but since the trial did not complete and given the carryover effect in the crossover design, this study should be considered as supportive and cannot be considered an independent adequate and well controlled trial supporting the application.

- Studies in less closely related diseases, but where the general purpose of therapy is similar

Eculizumab is approved for two other indications, treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis and the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. While it is not possible to know which effects confer the particular effect in each case, the sponsor has provided adequate direct evidence to suggest the drug inhibits complement (e.g., the complete inhibition of terminal complement (<20% cRBC hemolysis) was achieved in nearly all (54/62; 87%) patients treated with eculizumab in Study ECU-MG-301, and that free C5 concentration <0.5 µg /mL achieved in 57/62 (92%) of patients treated with eculizumab, and indirect evidence that that inhibition of complement in each case mediates the effect (e.g., and that 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).

My own review of the Myasthenia Gravis literature suggested that the role for complement in the pathophysiology of MG is accepted in the scientific community and that dysregulation of this system leads to increased damage to the neuromuscular junction. I do not believe this is so well understood that the effectiveness can be linked to demonstration of the mechanism in e.g., an invitro setting,; however, this data I believe , is supportive.

Indication

The Division had encouraged the applicant to pursue (b) (4)

The applicant selected a population reasonably defined by medical history as being (b) (4) treatment of MG; however this was (b) (4) in their trial. The safety profile of the BLA submission suggests that at least in the vaccinated population, the risk of such infections is low (c.f., Section 9.5.1 of this review). Considering this and the trial design, I believe the indication should be for the treatment of Myasthenia Gravis, without (b) (4)

Influence of extrinsic and intrinsic factors on the effectiveness

I believe my analysis in Section 7.1.3 suggests that the treatment effect of eculizumab effects each of the recognized domains (ocular, breathing, etc...) measured in this application. Accordingly a claim of *generalized* Myasthenia Gravis (gMG) is supported.

9 Review of Safety

9.1. Safety Review Approach

This BLA received a 'standard' safety review consisting the following:

- A review of all adverse events, including their coding, seriousness, and severity;
- Laboratories and vital signs, checking for relative changes and values over clinically meaningful thresholds;
- Immunogenicity;
- Special safety concerns, including, in this case, included any facts relevant to the issue of encapsulated infections, which is a known issue for this drug.

9.2. Review of the Safety Database Overall Exposure

Total exposure to drug and placebo in the development program are presented in Table 22.

Table 22 Exposure to eculizumab in BLA 125166S422

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review			
Clinical Trial Groups	New Drug (n=133)	Active Control (n= 0)	Placebo (n=76)
Normal Volunteers	0	0	0
Treated in Controlled trials conducted for this indication[2]	75, (62[5a]+13[6])	0	76, (63[5b]+13[6])
Treated in all other than controlled trials conducted for this indication[3]	58[7]	0	0
Total treated in this indication	133	0	76
Treated in controlled trials conducted for other indications[4]	Not reviewed	Not reviewed	Not reviewed
Total Treated	133	0	76

[1] *study drug* means the drug being considered for approval.

(b)(4)

if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

[5] ECU-MG-301, a parallel group study; a = active, b = placebo during double blind period

[6] C08-001, a crossover study

[7] Patients initially randomized to placebo in Study 301. Treated with eculizumab in Study 302

A summary of the information pertinent to safety analysis for the three studies in this submission are included in Table 23.

Table 23 Studies Considered in the Safety Analysis of this Application

ECU-MG-301

Parameter	Dosing and Sampling Schedule
Dosing Regimen	Induction Phase: Either eculizumab 900 mg or matching placebo via IV infusion once a week (every 7 ± 2 days) for 4 weeks followed by eculizumab 1200 mg or matching placebo for the fifth dose (Week 4). Maintenance Phase: Either eculizumab 1200 mg or matching placebo via IV infusion every 2 weeks (every 14 ± 2 days) from the sixth dose onwards (Week 6). Supplemental Doses: If PE is given due to a clinical deterioration, either eculizumab 600 mg or matching placebo via IV infusion within 60 minutes after the end of each PE session. If PE was administered on a day of regularly scheduled study drug administration, patients received the regularly scheduled dose within 60 minutes after each PE session. Total duration of treatment: 26 weeks.
Adverse Events	Ongoing over the 26-week Study Period and at the Post-treatment Follow-up Visit
Chemistry and Hematology	Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 26, and Clinical Deterioration visit
12-Lead ECG	Week 26
Vital Signs	Day 1, Weeks 1 through 4 (weekly; each study visit), Weeks 6 through 26 (biweekly; each study visit), Post-treatment Follow-up Visit
C-SSRS	Day 1, Week 12, Week 26
ADA	Day 1, Week 4, Week 12, Week 26

ECU-MG-302

Parameter	Dosing and Sampling Schedule
Dosing Regimen	Blind Induction Phase: IV infusion of either (1) 4 vials eculizumab (300 mg/vial) on Day 1 and Week 2, and 4 vials of matching placebo on Weeks 1 and 3 (eculizumab/eculizumab arm); or (2) 3 vials eculizumab (300 mg/vial) + 1 vial matching placebo on Day 1 and Weeks 1, 2, and 3 (placebo/eculizumab arm). Open-Label Maintenance Phase: Eculizumab 1200 mg via IV infusion every 2 weeks (every 14 ± 2 days) from the fifth dose onwards (Week 4). Supplemental Doses: If PE is given due to a clinical deterioration, either eculizumab 600 mg or matching placebo via IV infusion within 60 minutes after the end of each PE session. If PE was administered on a day of regularly scheduled study drug administration, patients received the regularly scheduled dose within 60 minutes after each PE session. Total duration of treatment: Up to 4 years.
Adverse Events	Ongoing over the Study Period, and at the Post-treatment Follow-up Visit
Chemistry and Hematology	Day 1, Week 4, Week 8, Week 12, Week 26, Week 40, Week 52, Week 78, Week 130, Week 182, Week 208
12-Lead ECG	Day 1, Week 26, Week 52, Week 208
Vital Signs	Day 1, Weeks 1 through 4 (weekly; each study visit), Weeks 6 through 208 (biweekly; each study visit), Post-treatment Follow-up Visit
C-SSRS	Day 1, Week 12, Week 26, Week 40, Week 52, Week 78, Week 130, Week 182, Week 208
ADA	Day 1, Week 4, Week 12, Week 26, Week 40, Week 52, Week 78, Week 130, Week 182, Week 208

Study C08-001

Parameter	Dosing and Sampling Schedule
Dosing Regimen	For Treatment Period 1 and Period 2: Induction Phase: Patients received either eculizumab 600 mg or matching placebo via intravenous (IV) infusion once a week (every 7 ± 2 days) for 4 weeks followed by eculizumab 900 mg or matching placebo for the fifth dose 7 ± 2 days later. Maintenance Phase: Patients received either eculizumab 900 mg or matching placebo via IV infusion every 2 weeks (every 14 ± 2 days) for 6 doses. Wash-Out Period: 5 weeks in between Period 1 and Period 2
Adverse Events	Ongoing over both Treatment Periods, during the Washout Period, and follow-up phone call (Week 16 of Treatment Period 2 + 35 days)
Chemistry and Hematology	Screening Treatment Period 1: Day 1, Weeks 2, 4, 8, 12, and 16 Treatment Period 2: Day 1, Weeks 2, 4, 8, 12, and 16
12-Lead ECG	Screening Treatment Period 1: Week 16 Treatment Period 2: Week 16
Vital Signs	Screening Treatment Period 1: Day 1, Weeks 1 through 4 (weekly), Weeks 6 through 16 (biweekly) Washout Period: 2-3 weeks after Week 16 visit f Treatment Period 1 Treatment Period 2: Day 1, Weeks 1 through 4 (weekly), Weeks 6 through 16 (biweekly)
ADA	Treatment Period 1: Day 1, Weeks 4 and 16 Treatment Period 2: Day 1, Weeks 4 and 16

9.2.1. Adequacy of the safety database:

This section provides your conclusions with respect to the size and adequacy of the safety database considering exposure to the appropriate dose(s), duration of treatment, patient demographics, and disease characteristics with reference to the U.S, target population.

9.3. Adequacy of applicant's Clinical Safety Assessments

9.3.1. Issues Regarding Data Integrity and Submission Quality

Information in the safety section of the submission was adequate for analysis of this review.

9.4. Safety Results

9.4.1. Deaths

There were two deaths in or shortly after participation in the clinical development program. The applicant's narratives and associated information on these subjects is included below:

One patient (Patient (b) (6))[6] who had been treated in Study ECU-MG-301 subsequently died. This patient was a (b) (6), white female in the eculizumab arm, who 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 126, was transferred to the hospital ICU due to onset of MG crisis. She received several treatments with IVIg while in the ICU, and experienced additional adverse events 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 (b) (6) (90 days after discontinuing from the study). At the time of these events, the patient was receiving the following concomitant medications: alprazolam, citalopram, famotidine, human mixtard, insulin human, mycophenolate mofetil, 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.

A patient (Patient (b) (6)) was reported to have died after the (b)(6) (b)(6) for the interim analysis of Study ECU-MG-302. This patient had a case of suspected CMV hepatitis, multi-organ failure, and sepsis.

9.4.2. Serious Adverse Events

[6] See also Patient Disposition and Protocol Violations sections for Trial 301 which mention this subject.

Of the 125 patients in Study ECU-MG-301, 27 (21.6%) reported a total of 50 SAEs (33 in the placebo arm and 17 in the eculizumab arm). The number (percentage) of patients reporting one or more treatment-emergent serious adverse events (TESAEs) was 18 (28.6%) in the placebo arm compared to 9 (14.5%) in the eculizumab arm. Consistent with these findings, there were 27 patients with hospitalizations; 18 patients with hospitalization were treated with placebo compared with 9 patients treated with eculizumab. By SOC, Infections and Infestations were the most frequently reported SAEs, experienced by 6 (9.5%) patients in the placebo arm and 3 (4.8%) patients in the eculizumab arm.

Table 24 Treatment Emergent Serious Adverse Events (TESAEs) of Special Interest by MedDRA SOC/Preferred Term by Treatment Arm in Study ECU-MG-301 – Safety Set

System Organ Class Preferred term	Placebo (N = 63)		Eculizumab (N = 62)		Total (N = 125)	
	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)	11	8 (6.4)
Infections and infestations	7	6 (9.5)	4	2 (3.2)	11	8 (6.4)
Bacteraemia	0	0 (0.0)	1	1 (1.6)	1	1 (0.8)
Diverticulitis	0	0 (0.0)	2	1 (1.6)	2	1 (0.8)
Endocarditis	0	0 (0.0)	1	1 (1.6)	1	1 (0.8)
Gastroenteritis	2	1 (1.6)	0	0 (0.0)	2	1 (0.8)
Tonsillitis	1	1 (1.6)	0	0 (0.0)	1	1 (0.8)
Upper respiratory tract infection	2	2 (3.2)	0	0 (0.0)	2	2 (1.6)
Urinary tract infection bacterial	1	1 (1.6)	0	0 (0.0)	1	1 (0.8)
Varicella	1	1 (1.6)	0	0 (0.0)	1	1 (0.8)

Source: Study ECU-MG-301 CSR Table 14.3.2.1.1.7.3; Module 2.7.4.2.1.12

Serious adverse events of Myasthenia Gravis were reported for 8 (12.7 %) placebo treated patients and in 5 (8.1 %) eculizumab-treated patients. MG crisis was reported for 1 eculizumab-treated patient (1.6 %).

My reanalysis of the AE datasets with coding adjusted was yielded similar results with SAE Pyrexia also appearing to be greater than placebo. Two (3%) events in the eculizumab occurred for SAE Pyrexia, whereas there were none on placebo. All of the other events in the eculizumab arm had one event (2%) and none for placebo.

The incidence of SAEs in the eculizumab/eculizumab arm of Study ECU-MG-302 (16.4%) was similar to that of the eculizumab arm in Study ECU-MG-301 (14.5%). The incidence of TESAEs in the placebo/eculizumab arm in Study ECU-MG-302 (15.4%), about half that of the incidence in the placebo arm in Study ECU-MG-301 (28.6%). My own reanalysis is presented in

Table **25**.
Notably, while the rates of SAEs are low, those associated with infection are higher in the arm receiving eculizumab for the longest time (eculizumab/eculizumab), suggesting there is not a tolerance to the adverse effect that is one of those of primary concern for this drug.

Table 25 Incidence of SAEs in Study 302 by prior treatment in Study 301

Prior treatment ➔		eculizumab in Study 301		Placebo in Study 301	
Final PT	N Patients w event	N	%	N	%
Myasthenia gravis crisis	7	4	7	3	5
Gastroenteritis	1	0	0	1	2
Headache	1	0	0	1	2
Loss of consciousness	1	0	0	1	2
Malignant melanoma in situ	1	0	0	1	2
Pulmonary embolism	1	0	0	1	2
Syncope	1	0	0	1	2
Tonsillitis	1	0	0	1	2
Influenza	2	2	4	0	0
Acute kidney injury	1	1	2	0	0
Gastrointestinal haemorrhage	1	1	2	0	0
Intestinal obstruction	1	1	2	0	0
Ovarian cyst	1	1	2	0	0
Pneumonia	1	1	2	0	0
Pseudomonal sepsis	1	1	2	0	0
Respiratory syncytial virus infection	1	1	2	0	0
Small intestinal obstruction	1	1	2	0	0

9.4.3. **Dropouts and/or Discontinuations Due to Adverse Effects**

In Study ECU-MG-301, 7 patients who were treated with either placebo or eculizumab discontinued from the study: 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 (Table 26).

Table 26 Discontinuations from Studies 301 and 302

Study	Patient ID	Study Day of Discontinuation*	Reason for Discontinuation	Treatment Arm
ECU-MG-301	(b) (6)	80 (80/32)	SAE (Bacteremia)	Eculizumab
ECU-MG-301		127 (127/99)	SAE (Intestinal perforation)	Eculizumab
ECU-MG-301		128 (128/126)	SAE (MG; MG crisis)	Eculizumab
ECU-MG-301		85 (85/70)	SAE (Prostate cancer; Metastases to bone)	Eculizumab
ECU-MG-301		37 (37/22)	Patient withdrew consent citing failure to improve to her satisfaction	Eculizumab
ECU-MG-301		28 (28/0)	Patient withdrew consent	Placebo
ECU-MG-301		71 (71/0)	Patient withdrew consent	Placebo
ECU-MG-302		192 (387/324)	SAE (MG)	Eculizumab/Eculizumab
ECU-MG-302		108 (300/286)	Patient withdrew consent	Eculizumab/Eculizumab
ECU-MG-302		161 (356/343)	Other	Eculizumab/Eculizumab
ECU-MG-302		62 (258/197)	Patient withdrew consent	Eculizumab/Eculizumab
ECU-MG-302		183 (379/379)	Physician decision	Eculizumab/Eculizumab
ECU-MG-302		113 (309/99)	Patient withdrew consent	Placebo/Eculizumab
ECU-MG-302		154 (359/125)	Patient withdrew consent	Placebo/Eculizumab

* 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
Source: Study ECU-MG-301 CSR Listing 16.2.1.1.5 and Listing 16.2.7.2.3; Study ECU-MG-302 CSR Listing 16.2.1.1.2 and Listing 16.2.7.2.3; Module 2.7.4.2.1.13

The applicant's narratives (in their wording and format) describing patients that discontinued are presented below:

- Study 301, discontinuations from the eculizumab arm

  • Patient (b) (6) (SAE MG crisis)

  The patient experienced worsening of her MG and was admitted to the hospital on (b) (6) (Study Day 112) for plasmapheresis. She was transferred to the intensive care unit on (b) (6) (Study Day 127) for MG crisis. The patient discontinued from the study on (b) (6) (Study Day 128). On (b) (6) (89 days after the last dose of study drug and 215 days after the first dose of study drug), the patient's condition continued to deteriorate, she developed bradycardia then asystole, and died; no autopsy was performed and a death certificate was not provided. The study drug (eculizumab) was discontinued due to the event of MG crisis; the last dose was administered on (b) (6) (Study Day 126).

  • Patient (b) (6) (SAE Intestinal perforation)

  On (b) (6) (Study Day 107), the patient experienced onset of diverticulitis and intestinal perforation, his second episode of each during the study (the patient also had history of diverticulitis prior to enrolling in the study [beginning in 2005]). The patient was receiving prednisone and aspirin throughout the study (mycophenolate mofetil was discontinued after the first episode of intestinal perforation and diverticulitis). The patient was admitted for conservative management with antibiotic therapy, including intravenous metronidazole and piperacillin-tazobactam, and oral amoxicillin and metronidazole. On (b) (6) (Study Day 112), the patient was discharged from the hospital and the events were considered resolved. The study drug (eculizumab) was discontinued as a result of the event of intestinal perforation. The association of increased risk of gastrointestinal ulceration and perforation with steroid therapy and with mycophenolate mofetil is well established. Similarly, regular use of aspirin or NSAIDs is associated with an increased risk of diverticulitis and diverticular bleeding. [In post-discontinuation follow up, …] Patient (b) (6) was seen in the clinic on (b) (6) by a nurse practitioner, at which time he reported his diplopia had "essentially resolved since August and eyes were wide open". He further reported that for the

previous "3 months" he had only been using his BiPAP at night, that his legs were still "a little weak", and he was using a cane; he reported his arms "were strong". In (b) (6), he was seen by his primary neurologist who documented that the patient said he had "slid back" and was now using BiPAP 12-13 hours/day, his legs were weaker, he had frequent diplopia, and he had intermittent dysphagia. At the time, he remained off Cellcept and was still on prednisone 25 mg daily. In (b) (6) he was evaluated for a separate study but could not pass screening due to respiratory weakness. By (b) (6), his prednisone was increased to 40 mg daily. He was referred to a major hospital closer to him where a neuromuscular-trained neurologist could see him but, as of (b) (6), the patient had not seen this neurologist. The patient reported that he had been hospitalized in (b) (6) for another episode of diverticulitis and bowel perforation.

- Patient (b) (6) (SAE Prostate cancer)

This patient had a medical history of benign prostatic hyperplasia. On (b) (6) (Study Day 84), the patient underwent a computerized tomography scan of the abdomen, which showed the following: a large osteolytic lesion of the pelvic bone with soft tissue expansion (9 × 7 cm left), an enlarged prostate gland, infiltration of the bladder, and lymphadenopathy in the retroperitoneum, lower pelvis, and inguinal region. On (b) (6) (Study Day 85), scintigraphy of the bones was performed, and the patient was diagnosed with adenocarcinoma of the prostate gland (prostate cancer) with bone metastases. The study drug (eculizumab) was discontinued in response to the event of prostate cancer. The events of prostate cancer and bone metastases both remained unresolved at the time of database lock.

Post-Discontinuation Follow Up

As of (b) (6), Patient (b) (6) was in the care of the department of oncology receiving palliative treatment. His MG status had worsened since leaving Study ECU-MG-301: his eyelids drooped, he could not speak or swallow in the afternoon, had severe weakness of his extremities, and could barely walk 50 meters.

- Patient (b) (6) (SAE Bacteraemia)

On (b) (6) (Study Day 41), the patient presented to the emergency room with fever (39.0°C), chills, tachycardia, hyperhidrosis, a habitual cough, expectoration with white mucus, and headache. The patient was admitted to the hospital for further evaluation and was administered intravenous antibiotic therapy from (b) (6) (Study Day 41) to (b) (6) (Study Day 70). Blood cultures were positive for Moraxella lacunata. On (b) (6) (Study Day 58), repeat blood cultures were free of Moraxella lacunata. On (b) (6) (Study Day 62), the patient was discharged from the hospital. On (b) (6) (Study Day 80), 48 days after her last dose of study drug (eculizumab), the patient was withdrawn from the study due to the event of bacteremia.

Generalized MG is associated with impairment of the respiratory musculature and this patient demonstrated shortness of breath at rest. In addition, the causative association between cigarette smoking and chronic obstructive pulmonary disease is well established, and the patient had a chronic cough and expectoration with white mucus at Baseline that was attributed to her cigarette smoking. Both of the refractory gMG and the cigarette smoking placed this patient at substantive risk for worsened respiratory impairment/disease – a condition strongly associated with the occurrence of Moraxella infection.

Post-Discontinuation Follow Up

Prior to the study, the patient was home-bound, unable to walk any significant distance, and required assistance for most activities. Her social life was markedly curtailed; double vision was also problematic and prevented her from reading or watching television, particular in the evening when she was most weak and fatigued. At the end of her participation in the study, she was able to read the morning paper, watch television, and shower and dress herself without help. Her lower extremity strength had improved such that she was able to walk through her village. Following discontinuation from Study ECU-MG-301, Patient (b) (6) progressively worsened, requiring her prednisone dose to be increased to 60 mg daily; consequently, tacrolimus 3 mg/12 h was started. She exhibited clear improvement with tacrolimus, and the dose of prednisone was progressively decreased to 15 mg on alternate days. On (b) (6), the patient informed the PI of a clinical worsening in the context of starting antibiotic therapy (streptomicine plus metronidazole) after a tooth extraction and, following examination by the PI, the patient was hospitalized for IVIG treatment. Currently, the patient is improving and is on a regimen of tacrolimus 3 mg/12 h and prednisone 15 mg on alternate days.

• Patient (b) (6) (Withdrawal)
The patient in the eculizumab arm who withdrew consent cited the reason for withdrawal as her dissatisfaction with not improving.

Two patients in the placebo arm (Patient (b) (6) and Patient (b) (6)) withdrew consent. Within the week prior to their withdrawal, both of these patients were hospitalized for MG deterioration.

As of the clinical database cutoff 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. One patient discontinued due to an AE in the eculizumab/eculizumab arm. A narrative for this patient is included below:
• Patient (b) (6) (SAE Myasthenia gravis; not related to study drug)
On (b) (6) (Study Day 146), the patient was hospitalized and placed in the intensive care unit where she required intubation and other respiratory support after experiencing acute respiratory failure related to MG crisis. She had skipped her protocol visit the previous week because she was suffering from pharyngitis in the context of a cold/flu. On (b) (6) (Study Day 149), the investigator spoke to the neurologist at the hospital and it was decided to administer intravenous IVIg and intravenous methylprednisolone. On (b) (6) (Study Day 156), the patient underwent tracheostomy. The patient was discharged from the hospital and the event was considered resolved on (b) (6) (Study Day 176). The patient withdrew from the study following this event. Both the Investigator and Alexion considered the event of MG to be not related to eculizumab.

Two patients from the eculizumab/eculizumab arm, (Patient (b) (6) and Patient (b) (6)) withdrew consent, 1 patient discontinued from the study due to physician decision (Patient (b) (6)), and a fourth patient (Patient (b) (6)) discontinued for other reasons.
The 3 patients who had either withdrawn consent or discontinued for other reasons were each experiencing one or more AEs at the time of discontinuation; however, the reason for withdrawal was not considered due to an AE.

Two patients from the placebo/eculizumab arm (Patient (b) (6) and Patient (b) (6)) 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.

9.4.4. **Significant Adverse Events**

The incidence of adverse events of severe intensity was generally low. Only one subjects experienced each event in Study 301 where the percent on eculizumab was greater than placebo (Table 27).

Table 27 Adverse Events of Severe Intensity where % Eculizumab Is Greater Than Placebo (Study 301)

Final PT	N Rows	N(Eculizumab)	% ecu	N(Placebo)	% P
Atelectasis	1	1	2	0	0
Bacteraemia	1	1	2	0	0
Critical illness myopathy	1	1	2	0	0
Critical illness polyneuropathy	1	1	2	0	0
Diverticulitis	1	1	2	0	0
Endocarditis	1	1	2	0	0
Intestinal perforation	1	1	2	0	0
Lymphocyte count decreased	1	1	2	0	0
Metastases to bone	1	1	2	0	0
Musculoskeletal pain	1	1	2	0	0
Post procedural fistula	1	1	2	0	0
Prostate cancer	1	1	2	0	0
Pyrexia	1	1	2	0	0
Weight decreased	1	1	2	0	0

The patterns and conclusions regarding the adverse events of severe intensity in the 302 study seem similar to those from 301(
Table 28).

Table 28 Incidence of Adverse Events of Severe Intensity in 302

Final PT	N Patients	N (Eculizumab)	% who were on ecu in 301	N (Placebo)	% who were on pbo in 301
Myasthenia gravis crisis	7	4	7	3	5
Gastroenteritis	1	0	0	1	2
Headache	1	0	0	1	2
Loss of consciousness	1	0	0	1	2
Malignant melanoma in situ	1	0	0	1	2

Final PT	N Patients	N (Eculizumab)	% who were on ecu in 301	N (Placebo)	% who were on pbo in 301
Pulmonary embolism	1	0	0	1	2
Syncope	1	0	0	1	2
Tonsillitis	1	0	0	1	2
Influenza	2	2	4	0	0
Acute kidney injury	1	1	2	0	0
Gastrointestinal haemorrhage	1	1	2	0	0
Intestinal obstruction	1	1	2	0	0
Ovarian cyst	1	1	2	0	0
Pneumonia	1	1	2	0	0
Pseudomonal sepsis	1	1	2	0	0
Respiratory syncytial virus infection	1	1	2	0	0
Small intestinal obstruction	1	1	2	0	0

9.4.5. **Treatment Emergent Adverse Events and Adverse Reactions**

There were 1415 AEs in both 301 and 302 study; 913 AEs occurred in the controlled 301 study using 606 unique AE PTs.

Before verifying the incidence of AEs reported by the applicant, I checked the coding for over-lumping or splitting of terms.

1) Steps in cleaning AE dataset (ADAE)
   a) Before separating the 2 trials (301 & 302), I consolidated AE terms
   b) I changed 33 unique terms in 141or ~ 10% of events; some terms were consolidated because of similarity of other terms and not because they were coded 'wrong.'

Table 29 Terms in the AE Dataset that were Modified by Medical Officer in Review

N Events Affected	AEDECOD	Proposed New PT
1	Normochromic normocytic anaemia	anaemia
1	Vertigo positional	Vertigo
1	Conjunctivitis allergic	Conjunctivitis
1	Abdominal pain lower	Abdominal pain
5	Abdominal pain upper	
1	Gastrointestinal pain	
1	Diarrhoea haemorrhagic	Gastrointestinal haemorrhage
7	Influenza like illness	Influenza

N Events Affected	AEDECOD	Proposed New PT
2	Infusion site pruritus	Infusion site reaction
3	Injection site erythema	
3	Peripheral swelling	Oedema peripheral
1	Escherichia urinary tract infection	Cystitis
2	Helicobacter gastritis	Gastritis
8	Gastroenteritis viral	Gastroenteritis
2	Gastrointestinal infection	
1	Genital herpes simplex	Herpes-related infection
3	Herpes zoster	
6	Oral herpes	
2	Lower respiratory tract infection	Respiratory tract infection
2	Viral upper respiratory tract infection	
2	Body tinea	Tinea infection
1	Tinea infection	
3	Cystitis	Urinary tract infection
1	Drug dose omission	Drug administration error
2	Wrong drug administered	Medication error
3	Lymphopenia	Lymphocyte count decreased
1	Neutrophil percentage increased	Neutrophil count increased
3	Asthenia	Muscular weakness
13	Myalgia	Musculoskeletal pain
13	Pain in extremity	
44	Myasthenia gravis	Myasthenia gravis crisis
1	Alopecia areata	Alopecia
1	Dermatitis acneiform	Dermatitis

c) Isolate events starting in ECU-MG-301 study

An incidence table was generated with a 5% cutoff (and greater than placebo for reporting). Percentages were rounded to the nearest integer. Those terms (3 highlighted yellow), where the whole number were the same, were omitted from the table for Section 6.1 but are included here for completeness.

Table 30 Common Adverse Events with an Incidence Greater than 5% and then Placebo

Final PT	Final SOC	N Rows	N(Eculizumab)	%ECU	N(Placebo)	% PBO
Musculoskeletal pain	Musculoskeletal and connective tissue disorders	14	9	15	5	7.9
Diarrhoea	Gastrointestinal disorders	16	8	13	8	13
Abdominal pain	Gastrointestinal	7	5	8.1	3	4.8

Final PT	Final SOC	N Rows	N(Eculizumab)	%ECU	N(Placebo)	% PBO
	disorders					
Contusion	Injury, poisoning and procedural complications	7	5	8.1	2	3.2
Dizziness	Nervous system disorders	10	5	8.1	5	7.9
Herpes-related infection	Infections and infestations	7	5	8.1	1	1.6
Oedema peripheral	General disorders and administration site conditions	8	5	8.1	3	4.8
Urinary tract infection	Infections and infestations	10	5	8.1	5	7.9
Pyrexia	General disorders and administration site conditions	6	4	6.5	2	3.2

ECU-MG-302

Adverse events from the 302 trial were obtained from the dataset described above for ECU-MG-301.

Table **31** demonstrates those AEs occurring in more than 10% of the 302 population (N = 113; above the thick bar) and those events that occurred at less than 10% that this reviewer considered to be potentially clinically significant (below black bar).

Table 31 Adverse Events Occurring at > 10% and those of Note from Study ECU-MG-302

AEDECOD	% Eculizumab
Headache	26
Nasopharyngitis	24
Diarrhoea	15
Arthralgia	12
Upper respiratory tract infection	11
Nausea	10
Infusion related reaction	8
Atrial fibrillation	4
Squamous cell carcinoma	4

AEDECOD	% Eculizumab
Acute myocardial infarction	2
Cardiac failure	2
Haematochezia	2
Lymphopenia	2
Rash papular	2
Sepsis	2
Acute respiratory failure	.9
Cardiac ventricular thrombosis	.9
Carotid artery stenosis	.9
Cholinergic syndrome	.9
Coagulopathy	.9
Colon cancer	.9
Disseminated intravascular coagulation	.9
Histiocytosis haematophagic	.9
Intra-abdominal haematoma	.9
Intraductal papillary mucinous neoplasm	.9
Lymphadenopathy mediastinal	.9
Metabolic encephalopathy	.9
Myocardial ischaemia	.9
Neuroendocrine carcinoma	.9
Pseudomonal sepsis	.9
Renal cyst haemorrhage	.9
Septic shock	.9
Small intestinal obstruction	.9
Transient ischaemic attack	.9

I further evaluated the AEs in the 302 study for those that occurred in the subjects transitioning from the placebo arm in the 301 trial at a rate 5% greater than those in the 301 eculizumab arm. I am not generally concerned by the nature of those events that seem to emerge on treatment (switching from placebo to eculizumab), they are generally the same as the initial initiation of treatment with eculizumab in the 301 study; however, there seemed to be more events considered to be 'infusion reactions' (Table 32). These do not seem of the same type or magnitude as 'cytokine release syndrome' which are also referred to with the name (infusion reaction) but of notably more intensity and sequelae. Arthralgias and symptoms of respiratory infections (e.g., Cough, Bronchitis, Influenza) seem to increase over time when one compares the incidence on prior eculizumab to placebo,

Table 32 Adverse events >10% in Study 302 by Prior Treatment from the 301 study.

		N | % in Population with Treatment from Study 301			
AEDECOD	N AEs (Total)	eculizumab		placebo	
Nasopharyngitis	28	15	27	13	22

Headache	31	11	20	20	34
Arthralgia	14	10	18	4	7
Diarrhoea	17	9	16	8	14
Myasthenia gravis	17	9	16	8	14
Upper respiratory tract infection	13	8	15	5	9
Cough	11	7	13	4	7
Bronchitis	10	6	11	4	7
Influenza	10	6	11	4	7
Pain in extremity	12	5	9	7	12
Myalgia	11	4	7	7	12
Nausea	12	4	7	8	14
Infusion related reaction	9	3	5	6	10
Back pain	9	2	4	7	12
Oropharyngeal pain	8	2	4	6	10

Laboratory Findings

Laboratories were evaluated through shift charts and assessment of individual outlier values.

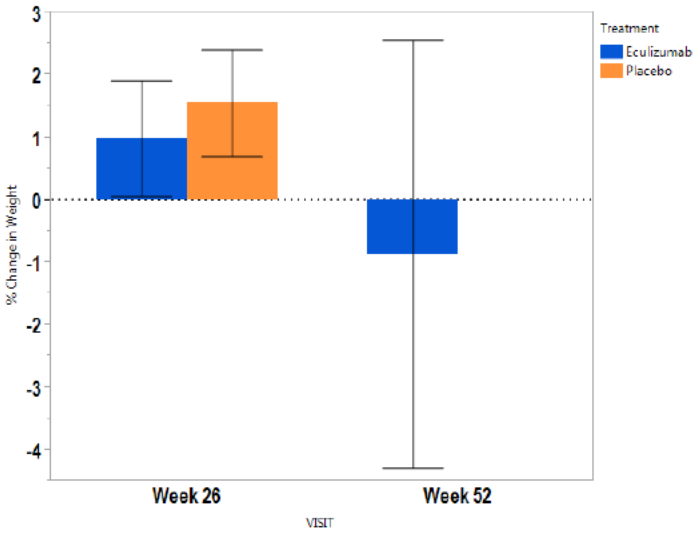
- These included evaluations of :
- Weight
- Blood Pressure (systolic; BPsys)
- Blood Pressure (diastolic; BPdias)
- Heart Rate

No signals related to laboratories were detected in the eculizumab arm when evaluated as the mean or median effect by treatment. Individual cases of abnormal results and some pertinent negative results by treatment arm are noted here.

9.4.6. **Vital Sign**

Weight
There was a small but insignificant difference (reduction) in the mean weight in the active treatment arm in the placebo-controlled 301 trial at Week 26 (Figure 22).

Figure 23 Mean change in weight by treatment in Study 301 (Week 26) and on eculizumab in the open label Study 302 (Week 52)

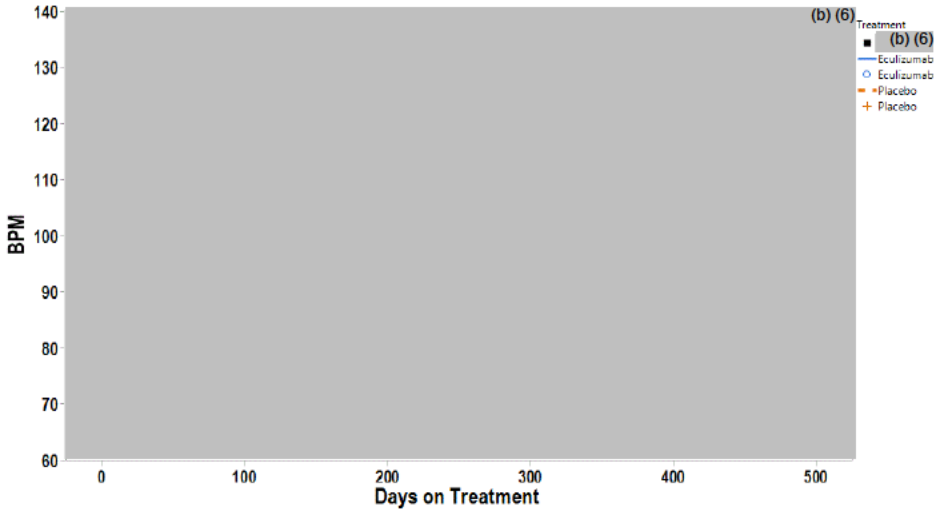


Only one subject ((b) (6)) subject sustained weight changes of clinical concern (> 10 or -10%) from 134 to 104 kg.

Pulse

There was no significant difference in the heart rate between treatment arms as assessed by ANOVA analysis; nominal P value for treatment by Visit was 0.9953. One subject had a notable increase in heart rate after switching from placebo to eculizumab (Figure 23).

Figure 24 Pulse rate of Subject (b) (6) by Time and Treatment in Studies 301 and 302

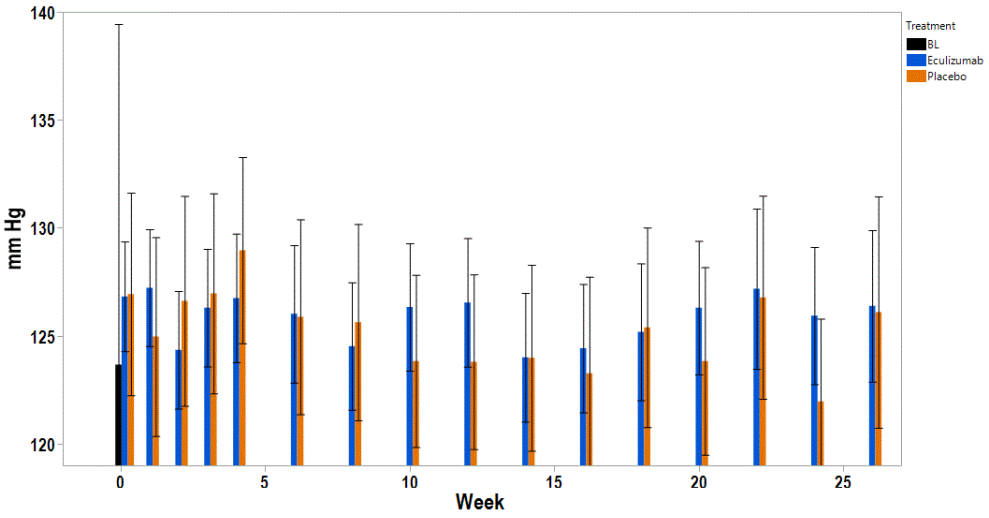


Blood Pressure

Systolic Blood Pressure (BPsys)

No significant differences were noted between treatment arms in systolic blood pressure. (Figure 24).

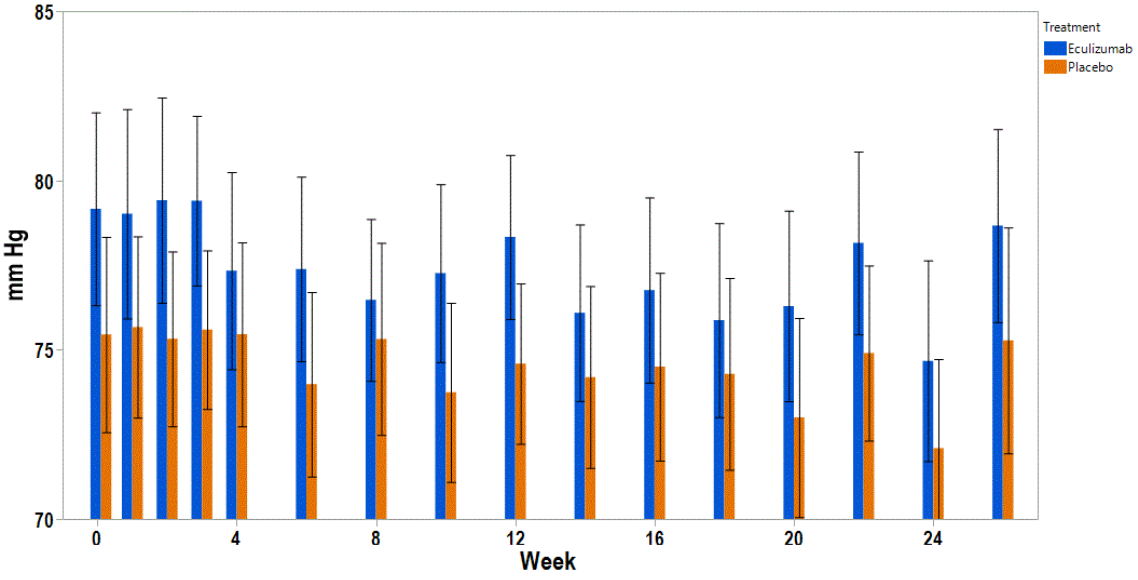
Figure 25 Mean Systolic Blood Pressure by Time and Treatment in Study 301



Diastolic Blood Pressure (BPdias)

There was not a significant difference in BPdias between treatment arms in the controlled portion of Study 301, although the eculizumab arm seemed higher as a group, at baseline and throughout the study (Figure 25).

Figure 26 Mean Diastolic Blood Pressure by Time and Treatment in Study 301



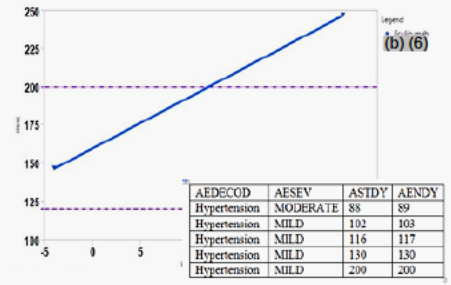
9.4.7. **Electrocardiograms (ECGs) including QT evaluation**

A Thorough QT analysis was not done as part of this application so my descriptions are based off of the ECGs performed during the 301 and 302 studies. ECG data were evaluated for changes in intervals (PR, QRS, QTcF) and reported Findings at both the by Treatment and on an individual basis. There were no notable differences in the treatment groups for any of these parameters. I did find several interval changes that warranted further investigation; these are presented in the figure below (Figure 26). Only one of the subjects on eculizumab had an adverse event related to arrhythmias, as evaluated by using the *SMQ Cardiac Arrythmias*; this subject is described below.

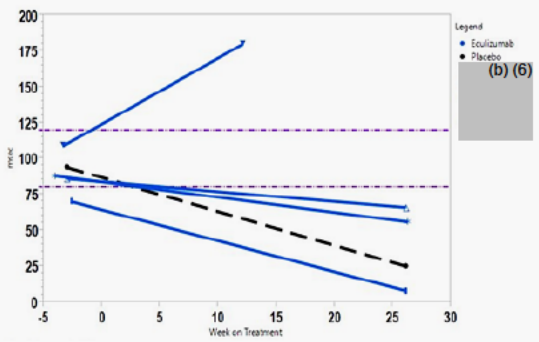
Of the patients who had ECG intervals that changed from normal to abnormal, very few had adverse effects that one would expect if these were clinically relevant or possibly related. No subject with these findings, e.g., of heart block, syncope, or conversion to some form of ventricular arrhythmia.

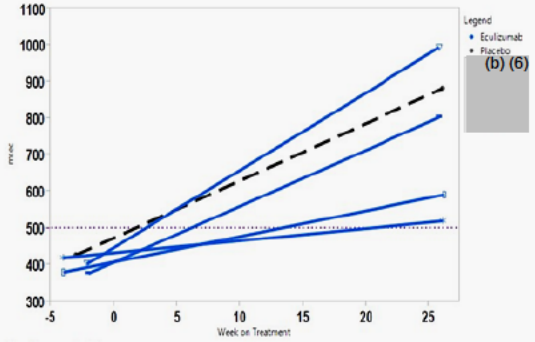
Figure 27 Individual Changes in Electrocardiogram analysis in the 301 and 302 Studies

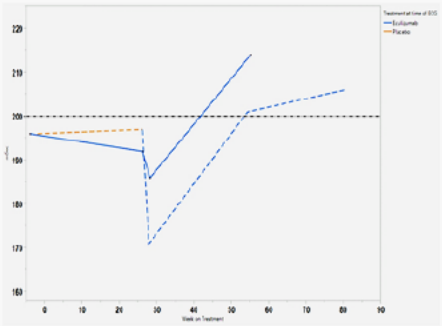
	PR	QRS	QTcF
301	Figure 24 Notable Change in the PR interval for Subjects in Study 301	Figure 25 Notable Change in the QRS interval for Subjects in Study 301	Figure 27 Notable Change in the QTcF interval for Subjects in Study 301
302	Figure 28 Notable Change in the PR interval for Subjects in Study 302	Figure 29 Notable Change in the QRS interval for Subjects in Study 302	Figure 30 Notable Change in the QTcF interval for Subjects in Study 302

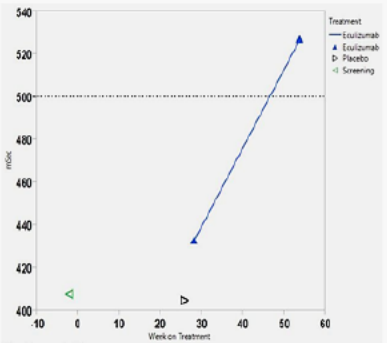


AEDECOD	AESEV	ASTDY	AENDY
Hypertension	MODERATE	88	89
Hypertension	MILD	102	103
Hypertension	MILD	116	117
Hypertension	MILD	130	130
Hypertension	MILD	200	200









9.4.8. **Immunogenicity**

Blood samples for human anti-drug antibody (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 neutralize the activity of eculizumab (ie, the ability of eculizumab to inhibit complement protein 5 [C5] cleavage by C5 convertase).
At Baseline in Study 301, 1 (1.6%) patient in the eculizumab arm was positive for ADA and no patients in the placebo arm were positive. At Weeks 4, 12, and 26, no patients in the eculizumab arm were positive for ADA. In the placebo arm, 2 (3.3%) patients, 1 (1.7%) patient, and 0 patients were positive for ADA at Weeks 4, 12, and 26, respectively. Only select patients (patients who discontinued from the study, patients who experienced clinical deterioration, and patients of Japanese descent) were analyzed for the interim CSR. Of the 27 total patients included in the analysis (14 from the placebo/eculizumab arm, and 13 from the eculizumab/eculizumab arm), none were positive for ADA up through Week 52 of the study.

No patient tested positive for ADA in Study C08-001.

9.5. **Analysis of Submission-Specific Safety Issues**

A primary concern when receiving this submission was the risk of infections, which is addressed in the section below.

9.5.1. **Risk for Infection from Serious Meningococcal Infections**

Soliris has a black box warning and a REMS regarding the risk for serious meningococcal infections. In a recent report to the MMWR newsletter[7], a CDC representative wrote that, "Health care providers should continue to follow recommendations from the Advisory Committee on Immunization Practices for eculizumab recipients to receive both MenACWY and MenB vaccines and could consider antimicrobial prophylaxis for the duration of eculizumab treatment to potentially reduce the risk for meningococcal disease," The report describes "16 cases of meningococcal disease in patients who received eculizumab in the United States from 2008 to 2016. Of those, 11 were caused by nongroupable *Neisseria meningitidis*. Fourteen patients had documented treatment with at least one dose of a meningococcal vaccine before disease onset, the researchers said.

Isolates taken from the 14 cases were mostly susceptible to six of seven antibiotics. However, 11 isolates were resistant to trimethoprim/sulfamethoxazole. One isolate was resistant to ciprofloxacin, and one to penicillin.

[7] **McNamara LA, et al. *MMWR Morb Mortal Wkly Rep.* 2017;doi:10.15585/mmwr mm6627e1.** as reported in https://www healio.com/infectious-disease/vaccine-preventable-diseases/news/online/%7Bf4de4ff3-17af-4f93-8b78-7962259534c7%7D/after-vaccine-meningococcal-disease-risk-still-high-with-soliris-use

Ten cases involved meningococcemia — the presence of the associated bacterium in the blood — without meningitis, the researchers said. Meningococcemia can cause relatively mild, influenza-like symptoms."[8]

"Health care providers should have a high index of suspicion for meningococcal disease in patients taking eculizumab who develop any symptoms consistent with either meningitis or meningococcemia, even if the patient's symptoms initially appear mild, and even if the patient has been fully vaccinated or is receiving antimicrobial prophylaxis."[5]

I performed my own specific analyses of the 301 and 302 studies for the risk of Neisseria and Aspergillus infections; these are presented in Table 33. In this analysis, similar to an SMQ analysis, I looked for several key preferred terms that are typical of these infections.

Table 33 Evaluation of Adverse Events Related to Encapsulated Organisms in Study 301

Level	MedDRA term	Proportion (%;N=63) Eculizumab	Proportion (%;N=63) Placebo	OR	P Value
SOC	Immune Disorders	0	6.35	0.104	0.119
	Infections and infestations	65.08	57.14	1.398	0.465
	Skin and subcutaneous tissue disorders	14.29	23.81	0.533	0.256
	Respiratory, thoracic and mediastinal disorders	12.7	20.63	0.559	0.339
Preferred terms associated with meningitis					
PT	Fever	6.35	3.17	2.068	0.68
	Headache	15.87	19.05	0.802	0.815
	Neck Pain[9]	4.76	3.17	1.525	1
	Nausea	12.7	14.29	0.873	1
	Vomiting	4.76	7.94	0.58	0.717
	Photophobia	1.59	0	3.048	1
	Fatigue	1.59	3.17	0.492	1
Preferred terms associated with Aspergillosis					
PT	Fever	6.35	3.17	2.068	0.68
	Chills[10]	1.59	6.35	0.238	0.365
	Dyspnoea	1.59	1.59	1	1
	Epistaxis	4.76	1.59	3.1	0.619
	Hemoptysis	0	0		

[8] As reported in https://www.healio.com/infectious-disease/vaccine-preventable-diseases/news/online/%7Bf4de4ff3-17af-4f93-8b78-7962259534c7%7D/after-vaccine-meningococcal-disease-risk-still-high-with-soliris-use

[9] Neck stiffness not reported
[10] Rigor not reported

Twelve subjects had 19 events from this SMQ (10.26%). One subject in the 301 and 302 trials had a narrow SMQ defined case of noninfectious meningitis but this subject was on placebo. **Overall, this suggests that there was not an increased risk of infections from the organisms listed in Table 33.**

9.6. Safety Analyses by Demographic Subgroups

While there were no signals of concern, an analysis by demographic factors was evaluated for imbalances. A graphical and numeric analysis along typical ISS parameters (duration, age, weight, etc…) was investigated by this medical reviewer. No issues of concern were raised by this analysis.

In general, more severe events were more common in the active treatment arm, with the possible exception of herpes-type infections (Figure 28). Incidence rates seem higher for males for PTs of Abdominal pain, contusion, and Oedema peripheral and other PTs are matched by gender (Figure 29). Regional evaluation did not reveal any significant trends.

Figure 28 Incidence of AEs by Duration and Treatment

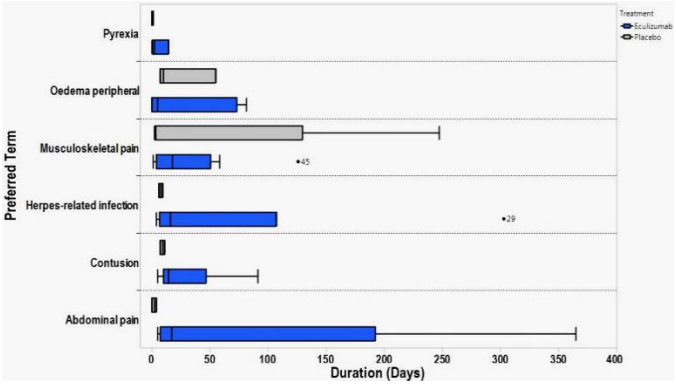


Figure 29 Incidence of AEs by Severity and Treatment

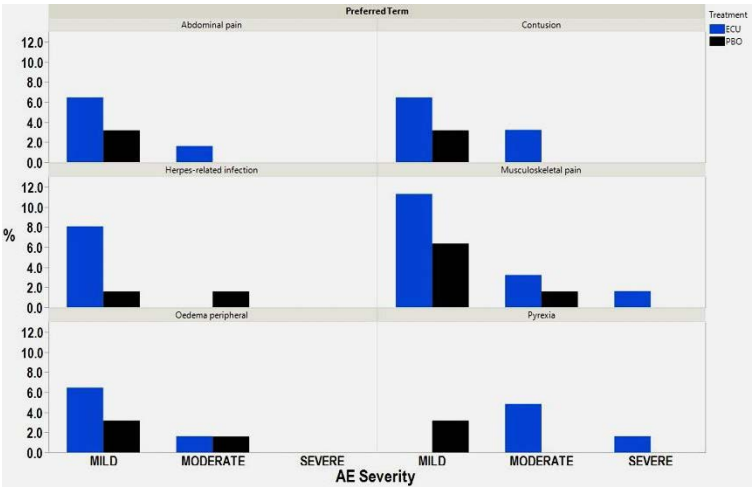


Figure 30 Incidence of AEs by Treatment and Gender

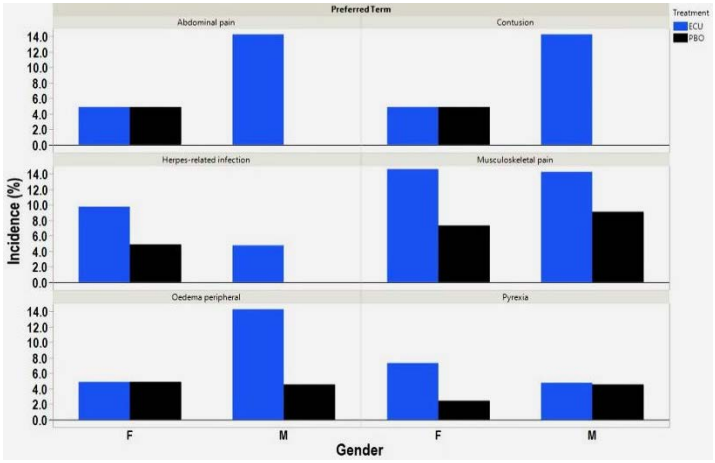
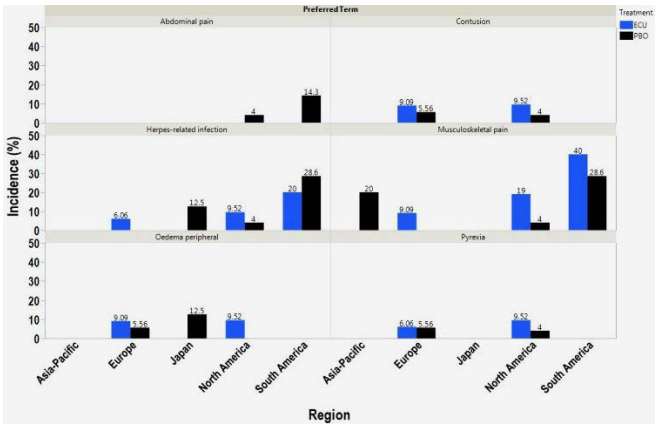


Figure 31 Incidence of AEs by Region and Treatment



Consideration of Special Populations

Pregnant Women

As of the end of Studies C08-001 and ECU-MG-301 and the clinical database cutoff date for Study ECU-MG-302 (01 Mar 2016), no pregnancies had been reported in the eculizumab clinical development program.

Geriatric patients

No apparent age-related differences were observed in the gMG studies; however, the applicant noted that the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

Pediatric Use

The safety and effectiveness of eculizumab therapy in gMG patients below the age of 18 have not been established.

Use in Patients with Hepatic Impairment
The safety and efficacy of eculizumab has not been studied in patients with hepatic impairment.

Use in Patients with Renal Impairment
According to previous labeling, no dose adjustment is required for patients with renal impairment. The clinical pharmacology review does not suggest need to change this labeling.

9.1. Safety in the Postmarket Setting

9.1.1. Safety Concerns Identified Through Postmarket Experience

The estimated exposure to Soliris in postmarketing experience since the first Marketing Authorization in Mar 2007, through to the data cutoff of 01 Oct 2016, is (b) (4) patient-years comprising (b) (4) patient-years and (b) (4) patient-years for PNH and aHUS, respectively. Based on a cumulative postmarketing exposure of approximately (b) (4) patient-years and 82 cumulative postmarketing reports of meningococcal infection to date, the reporting rate of patient susceptibility of meningococcal infection *(N. meningitidis)* is calculated to be 0.29-0.5 per 100 patient-years. Of the 82 cumulative postmarketing reports of meningococcal infection, 8 infections were fatal. The calculated fatal meningococcal infection rate is 0.03 per 100 patient-years.

9.1.1. Expectations on Safety in the Postmarket Setting

I do not expect the safety profile to change in the postmarketing period because

1. The drug has been on the US market since 2007, now with two indications, without major safety labeling changes.
2. No novel safety findings were detected in this review.

9.2. Integrated Assessment of Safety

The safety review of this application finds that there have not been new signals in this application, nor are there findings that mitigate previously labeled issues, such as the risk of infection.

The two deaths in this program seem consistent with the natural history of the disease, though a contributory role for the drug cannot be excluded. SAEs of concern are mostly described in the labeling; the patterns and conclusions regarding the adverse events of severe intensity seem similar to those in the preceding SAE analysis. Dropouts or treatment discontinuations were not due to issues concentrated in any specific area.

There were no differences in the mean incidence of abnormal labs or investigations (e.g., ECG), though there were individual cases that were required evaluation. Almost none of the abnormal investigations were accompanied by a report of an adverse event based on clinical signs.

10 Advisory Committee Meeting and Other External Consultations

An advisory Committee was not felt to be necessary for consideration of issues related to substantial evidence, safety, or risk:benefit considerations for the use of this drug in the MG population.

11 Labeling Recommendations

11.1. Prescribing Information

Modifications to the text of the labeling proposed by the applicant have been furnished by the clinical team. This included:

- Modifications to the numbers in the Table of Common Adverse events and listing of other events based on this reviewer's re-analysis with consolidated terms.
- Elimination of statements in the Warnings and Precautions section about (b) (4) that the OPDP representative believe were promotional and the Clinical review team agreed, noting the statements were also not adequately substantiated with evidence.

Text supplied by the applicant regarding immunogenicity in this population (Package Insert, Section 6.2) was considered acceptable.

12 Risk Evaluation and Mitigation Strategies (REMS)

12.1. Recommendations on REMS

Soliris has a REMS related to risks of infections from Neisseria meningitides and other encapsulated organisms. This review does not find any mitigation of the REMS and so it is recommended not to be modified.

13 Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended from this review.

14 Appendices

14.1. Scales

14.1.1. MGFA Clinical Classification(MGFA 2017)

Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.

Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
A. IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
A. IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
A. IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

14.2. Financial Disclosure

Covered Clinical Study: ECU-MG-301

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 302		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 2 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study 301 0 sponsor of covered study: Alexion		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes x	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	NoX (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No X (Request explanation from applicant)

14.3. Schedule of Events for Studies

Table 34 Study 301 Schedule of Events

Table 3: Study Design and Schedule of Assessments

Period /Phase	Screening	Induction					Maintenance											Post-treatment Follow-up	Clinical Deterioration [a]	UNS Visit [b]
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ ET [c]			
Study Weeks	2 – 4 Weeks	D1	W1	W2	W 3	W 4	W 6	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W24	W 26	+ 8 Weeks		
Informed Consent	X																			
Medical History	X																			
MG History [d]	X																			
MGFA Clinical Classification	X																			
Weight	X																X			
Height	X																			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination	X																			
12-Lead ECG	X																X			
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MG Therapy Status	X	X															X			
Adverse Event		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MG-QoL15	X	X				X		X		X		X		X			X	X		
Neuro-QoL Fatigue		X				X		X		X		X		X			X			
EQ-5D		X				X		X		X		X		X			X			
MG-ADL [e]	X	X	X	X	X	X		X		X		X		X			X	X	X	
QMG [f]	X	X	X	X	X	X		X		X		X		X			X	X	X	
NIF [f]	X	X	X	X	X	X		X		X		X		X			X	X	X	
MGC [f]	X	X	X	X	X	X		X		X		X		X			X	X	X	
MGFA PIS [g]						X				X							X	X		
C-SSRS		X								X							X			
AChR Ab	X									X							X		X	

Period /Phase	Screening	Induction					Maintenance												Clinical Deterioration [a]	UNS Visit [b]
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17/ ET [c]			
Study Weeks	2 – 4 Weeks	D1	W1	W2	W 3	W 4	W 6	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W24	W 26			
Clinical Lab Tests [h]	X	X				X		X		X		X		X			X		X	
Pregnancy Test [i]	X	X															X			
PK/PD, Free C5 [j]		B/P	T/P			T/P		T/P		T/P				T/P			T/P		X	
ADA [j]		B				X				X							X			
Medically Indicated Tests																			X	
Neisseria meningitidis Vaccination [k]	X																			
Patient Safety Information Card		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Randomization [l]		X																		
Study Drug Infusion [m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	

[a] Evaluation visit for MG crisis or clinical deterioration must have been performed as soon as possible within 48 hours of notifying the Investigator of the symptom onset. Additional evaluation visits could have been scheduled at the discretion of the Investigator.
[b] Unscheduled visit and procedures were performed at the Investigator's discretion and results were recorded in the eCRF.
[c] If a patient withdrew early from the study during the Study Period (Visits 2 through 17), an ET Visit was performed.
[d] MG history included:
1. Confirmation of MG diagnosis as defined by the protocol inclusion criterion #2
2. Recording the initial MG clinical presentation (ie, ocular MG [oMG] or gMG). If the initial clinical presentation was oMG, the time (date) to onset of gMG was record.
3. Recording the maximum MGFA classification since diagnosis, if available.
4. Recording whether the patient ever required ventilatory support since diagnosis.
5. Recording the number of hospitalizations, including number of ICU stay (days) and any ventilatory support associated with the hospitalization within the 2 years prior to screening.
6. Recording number and duration of all previous MG exacerbations or crises, the medication/therapy taken at the time of each exacerbation or crisis, and medication/therapy used for treatment of each exacerbation or crisis, if applicable.

[e] The MG-ADL should have been performed by a properly-trained evaluator, preferably the same evaluator, throughout the study. The recall period for MG-ADL was the preceding 7 days or since the previous visit if the visit interval was less than 7 days.
[f] The clinical assessments of QMG, NIF, and MGC should have been performed at approximately the same time of day and should have been performed by a properly-trained evaluator, preferably the same evaluator, throughout the study. If a patient was taking a cholinesterase inhibitor, the dose was required to be withheld for at least 10 hours prior to the QMG and MGC tests.
[g] The evaluation of MGFA PIS was to be performed by the PI or the same neurologist throughout the study.
[h] Clinical laboratory tests were performed at the central laboratory.

Table 35 Schedule of Events for C-08-001

	Screening	Treatment Period 1 – Induction Period					Treatment Period 1 – Maintenance Period					
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12
Study Week (Wk)	- 30 D	0	Wk 1 ± 2D	Wk 2 ± 2D	Wk 3 ± 2D	Wk 4 ± 2D	Wk 6 ± 2D	Wk 8 ± 2D	Wk 10 ± 2D	Wk 12 ± 2D	Wk 14 ± 2D	Wk 16 ± 2D
Informed Consent	X											
Medical History	X											
SF-36 and MG-QOL15 [1]		X				X		X		X		X
QMG, and NIF [2]	X	X	X	X	X	X	X	X	X	X	X	X
MG-ADL [2]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X											
ECG	X											X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
MG Therapy Status	X	X	X	X	X	X	X	X	X	X	X	X
MGFA Morbidity and Mortality	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
MGFA Post-Intervention Status [2]			X	X	X	X	X	X	X	X	X	X
Single Fiber Electromyography [3]		X										X
Clinical Laboratory (hematology, chemistry, urinalysis)	X	X		X		X		X		X		X
Serum Pregnancy Test [4]	X	X										X
Binding anti-AChR Abs	X	X				X		X		X		X
HAHA		X				X						X
PK and PD [5]		B	T/P			T/P		T/P		T/P		T/P
Vaccination: *N. meningitidis* [6]	X											
Randomization [7]		X										
Subject ID Card		X										
Dosing: Eculizumab (mg) or Placebo [8]		600	600	600	600	900	900	900	900	900	900	900

	Wash-Out	Treatment Period 2– Induction Period					Treatment Period 2– Maintenance Period						Follow-up Phone Call
Study Visit	13	14	15	16	17	18	19	20	21	22	23	24 / ET [9]	
Study Weeks (Wk)	Wk 2 - 3 after V 12	35 days after V12 0	Wk 1 ± 2D	Wk 2 ± 2D	Wk 3 ± 2D	Wk 4 ± 2D	Wk 6 ± 2D	Wk 8 ± 2D	Wk 10 ± 2D	Wk 12 ± 2D	Wk 14 ± 2D	Wk 16 ± 2D	35 days post last IP
SF-36 and MG-QOL15 [1]		X				X		X		X		X	
QMG and NIF [2]	X	X	X	X	X	X	X	X	X	X	X	X	
MG-ADL [2]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam												X	
ECG		X										X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	
MG Therapy Status	X	X	X	X	X	X	X	X	X	X	X	X	
MGFA Morbidity and Mortality	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
MGFA Post-Intervention Status [2]	X	X	X	X	X	X	X	X	X	X	X	X	
Single Fiber Electromyography [3]		X										X	
Clinical Laboratory (hematology, chemistry, urinalysis)		X		X		X		X		X		X	
Serum Pregnancy Test [4]		X										X	
Binding anti-AChR Abs		X				X		X		X		X	
HAHA		X				X						X	
PK and PD [5]		B	T/P			T/P		T/P		T/P		T/P	
Dosing: Eculizumab (mg) or Placebo [8]		600	600	600	600	900	900	900	900	900	900	900	

Footnotes for Tables 3 and 4: Schedule of Procedures and Assessments

[1] SF-36 and MG-QOL15 was to be administered before any other procedures

[2] The clinical assessments of QMG was to be performed by the same well trained study personnel e.g. neurologist or physical therapist throughout the trial. The MGFA Post-Intervention Status was to be performed by the PI or the same neurologist skilled in the evaluation of MG patients throughout the study. NIF and MG-ADL was to be performed by the same well trained evaluator throughout the trial

[3] Single fiber electromyography testing was to be performed at selected centers (see SFEMG Manual for details)

[4] Pregnancy tests were to be performed on all women of child bearing potential at Visits 1, 2, 12, 14 and 24. Pregnancy test may also be performed at any visit at the PI's discretion

[5] B = Baseline sample; T = trough sample; P = peak sample. Baseline and trough samples for PK and PD testing were to be taken 5 to 90 minutes before the study drug infusion. Peak samples for PK and PD testing were to be taken 60 minutes after the completion of the study drug infusion

[6] Patients were vaccinated for N. meningitidis 14 days prior to receiving the first eculizumab infusion

[7] Randomization of patient by the secure WebEZ randomization application and receipt of the first assigned investigational product kit occurred at least one week prior to Visits 2 and 12

[8] Patients who received matching placebo were infused with the same buffer components without the active ingredient (eculizumab)

[9] The Early Termination (ET) Visit included all the procedures scheduled for the Visit 24 for patient withdrawals from the study during the Treatment or Wash-Out periods

14.4. References

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/s/

CHRISTOPHER D BREDER
10/23/2017

NICHOLAS A KOZAUER
10/23/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166Orig1s422

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	125166
Support #:	1120
Drug Name:	Eculizumab
Indication(s):	(b) (4)
Applicant:	Alexion
Date(s):	Receipt date (12/23/2016); PDUFA due date (09/18/2017)
Review Priority:	Standard
Biometrics Division:	DBI
Statistical Reviewer:	Junshan Qiu, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader Hsien Ming (Jim) Hung, Ph.D., Division Director
Medical Division:	Division of Neurology
Clinical Team:	Christopher D Breder, M.D. Nicholas Kozauer, M.D.
Project Manager:	Michelle Mathers, Pharm. D.

Keywords: Analysis of Covariance; Worst Rank Analysis; Sensitivity Analysis

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1 EXECUTIVE SUMMARY

Study ECU-MG-301 shows that Eculizumab gives a statistically significant treatment effect on the primary endpoint of interest: change from baseline in Myasthenia Gravis – Activities of Daily Living (MG-ADL) total score at Week 26 ($p = 0.0140$ based on the worst rank analysis specified in SAP2). This analysis is deemed clinically justifiable to replace the primary analysis based on SAP3, per the discussion during the Type C meeting dated 9/14/2016 (see Section 5.1 for details).

2 INTRODUCTION

Study ECU-MG-301 titled "A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Eculizumab in Subjects with Refractory Generalized Myasthenia Gravis (gMG)" has been submitted to the FDA for the assessment of efficacy for Eculizumab.

2.1 Overview

Eculizumab (h5G1.1-mAb) is a humanized monoclonal Ab (mAb) that specifically binds with high affinity to the human terminal complement component 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, which are responsible for the inflammatory consequences of terminal complement activation. 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 neuromuscular junction (NMJ). Eculizumab can benefit refractory gMG patients who suffer from significant symptoms and persistent morbidities despite best available treatment with existing immunosuppressive therapies.

Eculizumab is approved for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) and treatment of atypical hemolytic uraemic syndrome (aHUS) in several countries, including the European Union and the USA, under the trade name Soliris®.

Alexion Pharmaceuticals, Inc. has completed a Phase 2, randomized, double-blind, placebo-controlled, crossover, pilot study (Study C08-001) to explore the safety and efficacy of eculizumab in 14 patients with AChR Ab+ refractory gMG. This 14-patient pilot study achieved the primary objective of demonstrating a significant clinical benefit of Eculizumab in patients with refractory gMG.

Study ECU-MG-301 is an adequate and well-conducted, placebo-controlled Phase 3 trial that employed MG-ADL as validated disease-specific instruments to demonstrate treatment effects of eculizumab in refractory gMG. Key information of Study ECU-MG-301 was presented in Table 2-1.

Table 2-1 Summary of the Studies for Statistical Review and Evaluation

Clinical Trial	Treatment/Number of patients enrolled	Trial Design/Treatment Duration and Dose per Protocol
ECU-MG-301	Eculizumab/ 62 Placebo/ 63	A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Eculizumab in Subjects with Refractory Generalized Myasthenia Gravis (gMG) has been submitted to the FDA for the assessment of efficacy for Eculizumab

	Variable	Endpoints
	MG-ADL total score	Primary: Change from Baseline in the MG-ADL total score at Week 26 of the Study Period for Eculizumab compared with placebo

2.2 Data Sources

At the time of review the locations of the primary endpoint data for the key studies were as follows.
ECU-MG-301:
\\CDSESUB1\evsprod\BLA125166\0572\m5\datasets\ecu-mg-301\analysis\adam\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

ECU-MG-301:
Date of first enrollment was 4/30/2014; date of end of treatment of last patient enrolled was 2/19/2016. The sponsor provided statistical analysis plans version 1.0 dated 6/26/2014, version 2.0 dated 3/30/2015 and version 3.0 dated 9/23/2015. Per the Clinical Data Review, the database was first locked on 4/15/2016. It was noted that there were 4 patients with inconsistent data entries for key parameters related to MG Clinical Deterioration, including use of rescue medication. The database was unlocked on 4/22/2016 to review the study data to confirm that all rescue medication use and Clinical Deteriorations had been appropriately captured for each patient. Inconsistency was identified for a total of 7 patients (Patient (b) (6) (Belgium; Placebo), Patient (b) (6) (UK; Placebo), Patient (b) (6) (Korea; Placebo), Patient (b) (6) (Argentina; Placebo), Patient (b) (6) (US; Placebo), Patient (b) (6) (Japan; Placebo), and Patient (b) (6) (UK; Placebo)). Pertaining to the database unlock for Study ECU-MG-301, we sent an Information Request via email on 5/22/2017 to ask the sponsor to clarify the following questions:

1. Did you only unlock the database for these subjects or an entire database containing all subjects?
2. What components (variables) of the study did this database contain?
3. Did this database have the capacity to provide an audit trail of all changes made at any time? If so, please describe the exact type of database and its properties related to audit trails for changes.
4. Provide a table for all subjects who had ANY changes in data entries made after the initial database lock, including the subject unique ID, variable changed, data before the change, data after the change, date of change, and rationale for change.

Table 3-1 Summary of Changes Made during the Database Unlock (4/22/2016) and the Impacts on Inference of Treatment Effect.

Subject #	Major Changes	Impact on efficacy evaluation
(b) (6)	Input administration of IVIG (i.e., rescue on (b) (6), (b) (6), and (b) (6)).	This patient completed the study. The impact is favoring treatment.
	Input clinical deterioration on (b) (6).	Last visit is (b) (6); ADL worsening date on (b) (6); complete the study. Probably there is no impact on treatment effect.
	Input rescue on (b) (6)	This patient completed the study. The impact is favoring treatment.
	Input clinical deterioration on (b) (6)	This patient was rescued on (b) (6). Since the changes were made after the rescue, there is no impact on treatment effect.
	Change adverse event date from (b) (6) to (b) (6); input adverse event on (b) (6); and input clinical deterioration on (b) (6) (unscheduled before Week 26) including MG-ADL, QMG scores, and MG Composite scale.	This patient completed the study without any rescue and ADL worsening is on (b) (6). Therefore, probably there is no impact on treatment effect.
	Input clinical deterioration on (b) (6) and input adverse event on (b) (6).	This patient was rescued on (b) (6); ADL worsening on (b) (6). Since the changes were made after the rescue, there is no impact on treatment effect.
	Input clinical deterioration on (b) (6) and (b) (6).	This patient was rescued on (b) (6) without ADL worsening. Since the changes were made after the rescue, there is no impact on treatment effect.

[Source: Reviewer]

The sponsor responded to our request on 5/25/2017 as follows.

1. Data collected via electronic data capture (EDC) were unlocked at the subject-level for a total of seven subjects (see response to Question 4 for details).
2. The study database within the Medidata Rave EDC system contained all eCRFs for the study. External data (e.g., safety laboratory data, PK/PD data) were managed outside of the EDC system and thus were not impacted in the study database unlock.
3. The Medidata Rave EDC platform supports electronic record and electronic signature (ER/ES) requirements including US 21 CFR part 11. As such, all changes made to the database are captured in the audit trail and available through an audit trail report. Any changes occurring to data post-lock required re-review and re-signature by the Investigator prior to re-locking those fields.
4. Specific records in the clinical database were unlocked for a total of 7 patients. Please refer to Table 1 in the IR response for the rationale of changes for each subject. The detailed data changes with identifiers and date of change are outlined in Table 2 in the IR response.

Per the email dated 8/7/2017, the field investigator was able to verify the data for the 7 subjects for whom data was changed when the database was unlocked. There was no evidence that any data was changed after the data was originally locked (other than the 7 subjects as indicated by the sponsor). The field investigator did not identify any issues related to data integrity. She is recommending an NAI classification.

The final study report states that the version 3.0 SAP was finalized prior to the final study database lock on 6/1/2016 and unblinding the study.

In summary, the quality and integrity of the submitted data were evaluated with respect to issues as follows:

- Whether it is possible to reproduce the primary analysis dataset, and in particular the co-primary endpoints, from the analysis data source
- Whether the applicant submitted documentation of data quality control/assurance procedures (see ICH E3,[1] section 9.6; also ICH E6,[2] section 5.1)
- Whether the blinding/un-blinding procedures were well documented (see ICH E3, section 9.4.6)
- Whether a final statistical analysis plan (SAP) was submitted and relevant analysis decisions (e.g., pooling of sites, analysis population membership, etc.) were made prior to un-blinding.

In all, the quality of the data that were submitted seems to be adequate in terms of the supporting documentation provided and usability.

3.2 Evaluation of Efficacy

3.2.1 Study ECU-MG-301

3.2.1.1 Study Design and Endpoints

This was a multi-center, double blind, prospective, randomized, placebo controlled study, assessing the efficacy and safety of Eculizumab for the treatment of patients with refractory gMG. A total of 114 investigational sites in 21 countries were initiated and 76 sites in 17 countries recruited at least one subject into the study. 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 enroll in the extension study). The total treatment time was 26 weeks.

Study Objective:
The primary objective of this trial was to assess the efficacy of Eculizumab as compared with placebo in the treatment of refractory gMG based on the improvement in the Myasthenia Gravis-specific Activities of Daily Living profile (MG-ADL).

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf
[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

Randomization:
A total of 126 patients were randomized in the study, 125 of whom received treatment and were analyzed. One patient, randomized to Eculizumab, discontinued prior to receiving any dose of study drug and, as defined in the protocol, was not included in any analysis group. Of the 125 treated patients, 62 were randomized to the Eculizumab arm and 63 were randomized to the placebo arm. The randomization was stratified based on MGFA clinical classification at the Screening Visit.

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

Efficacy Endpoints:
The primary efficacy endpoint was the change from Baseline in the MG-ADL total score at Week 26 of the Study Period for Eculizumab compared with placebo. The MG-ADL is an 8-item questionnaire that focuses on relevant symptoms and functional performance of activities of daily living (ADL) in MG subjects. Each item response is graded 0 (normal) to 3 (most severe). The range of total MG-ADL score is 0 to 24. MG-ADL will be performed at Screening, Day 1 (First Dose Date), Weeks 1-4, 8, 10, 12, 16, 20, and 26 or ET (Visits 2-6, 8, 10, 12, 14, and 17, or ET).

Secondary Endpoints:
• Change from Baseline in the QMG total score (i.e., total MG score as in ADEFF data) at Week 26
• Proportion of patients with ≥3-point reduction in the MG-ADL total score (i.e., total score as in ADEFF data) 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 Myasthenia Gravis Quality of Life 15-item Scale (MG-QoL15) (i.e., MG total Score as in ADEFF data) at Week 26
Analysis Population (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.

3.2.1.2 Study Statistical Methodologies

Efficacy Analyses:
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 covariates in the model. The rank strategy was as follows:

SAP Version 2:
In this analysis, the actual changes from baseline are ranked from highest (best improvement in MG-ADL score) to lowest (least improvement / most worsening in MG-ADL score) across all subjects who did not need rescue therapy. Then, any subject who needed rescue therapy would be given lower ranks. These lower ranks will be based on the time to rescue therapy from the start of investigational product (Day 1). The subject with the shortest time to rescue therapy would get the absolute lowest rank in the analysis and the subject with the longest time to rescue therapy would get a rank that is one lower than the lowest ranked subject without rescue therapy. To handle the patients who dropped out before Week 26 for all potential reasons but were not evaluated with respect to the need of rescue therapy even though they might, in fact, have met the criteria for rescue, the following strategy was proposed:

- Include patients who drop out before Week 26 who have a MG Crisis without rescue therapy in the rescue therapy ranking group, assigning ranks based on time from first dose date to date of the MG Crisis.

- Include patients who drop out before Week 26 who have worsening to a score of 3 or a 2-point worsening on any one of the individual MG-ADL items other than double vision or eyelid droop from baseline without rescue therapy in the rescue therapy ranking group, assigning ranks based on time from first dose date to date of first worsening to a score of 3 or a 2-point worsening on any one of the individual MG-ADL items, other than double vision or eyelid droop from baseline.

- If a patient drops out before Week 26 and has both an MG Crisis and a worsening to a score of 3 or a 2-point worsening on any one of the individual MG-ADL items other than double vision or eyelid droop from baseline without rescue therapy, then that patient will be included in the rescue therapy ranking group, assigning ranks based on the earlier time (shorter time) from first dose date to date of the MG Crisis or MG-ADL worsening.

- All other patients who drop out before Week 26 who don't meet the first two criteria above for rescue therapy will be ranked based on their last observation carried forward.

SAP Version 3:
Patients who die would get the worst ranks based on time from first IP dose to death date. Then, patients who experience MG crisis would be ranked next also using time from first IP dose to date of start of MG crisis. Then, patients needing rescue therapy for the other two reasons as well as patients who drop-out for any reason without rescue treatment would be ranked next after the MG Crisis/death patients using time from first IP dose in ECU-MG-301 to rescue therapy/dropout date. All other patients without rescue therapy or drop-out would be ranked based on their changes from baseline to Week 26 (or LOCF if Week 26 is missing). The actual changes from baseline are ranked from highest (best improvement in MG-ADL score) to worse

(least improvement / most worsening in MG-ADL score) across all subjects who did not dropout early, need rescue therapy, did not have MG Crisis or experienced death (due to any cause).

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 and p-values are presented.

For the secondary endpoints involved changes from Baseline (i.e., QMG, MGC, and MG-QoL15) were analyzed using a Worst-Rank ANCOVA as the primary analysis for a given secondary endpoint.

For the secondary endpoints: proportion of patients with ≥3-point reduction in the MG-ADL total score from Baseline to Week 26 with no rescue therapy, as well as the proportion of patients with a ≥5-point reduction in the QMG total score from Baseline to Week 26 with no rescue therapy, the Cochran-Mantel-Haenszel (CMH) test stratified by pooled randomization stratification variable was applied to compare Eculizumab versus placebo.

Multiplicity: The closed testing procedure was only used for the main analysis of each of the secondary efficacy endpoints. If statistical significance was not achieved for an endpoint ($p \leq 0.05$), then all endpoints of lower hierarchy were also not considered statistically significant, regardless of the calculated p-value.

Study Sites: Since a small number of patients are anticipated at each site, the study was randomized across centers and not within centers. As such, center will not be used as a covariate in the efficacy analyses.

Missing Data: Missing data for primary and secondary endpoints at Week 26 analyses were handled as described for the specific analyses.

Sensitivity Analyses:
A Worst-Rank ANCOVA sensitivity analysis was performed to compare the 2 treatment arms. In this sensitivity analysis, the actual change from Baseline in the MG-ADL total score at Week 26 was calculated for all patients who completed 26 weeks on study treatment without rescue therapy. For patients who completed the 26-week study but were missing Week 26 values, the LOCF was used. For patients who received rescue therapy or discontinued the study, the LOCF was used prior to rescue medication use, or time of discontinuation. Importantly, this sensitivity analysis retained the assignment of all rescue patients and discontinuation patients to the lowest ranks (i.e., ranked lower than patients who completed the 26-week study without rescue or discontinuation). The Baseline MG-ADL total score and the pooled randomization stratification variable were covariates in the model.

For the secondary endpoints involved changes from Baseline (i.e., QMG, MGC, and MG-QoL15), a Worst-Rank ANCOVA sensitivity analysis as the primary sensitivity analysis was performed to compare the 2 treatment arms.

A sensitivity analysis for the actual change from Baseline in the MG-ADL total score at Week 26 was also performed. Treatment arms were compared using an ANCOVA analysis using the actual change from Baseline in the MG-ADL total score at Week 26 with effects for treatment. The Baseline MG-ADL total score and the pooled randomization stratification variable were covariates in the model. Last observation carried forward was used for missing changes from Baseline at Week 26 for patients with a missing Week 26 assessment. Furthermore, for patients requiring rescue therapy, had MG crisis, or death, the last observation prior to the rescue therapy, MG crisis, or death was used for the Week 26 endpoint in the analysis.

For the secondary endpoints involved changes from Baseline (i.e., QMG, MGC, and MG-QoL15), an ANCOVA sensitivity analysis based on the actual change from Baseline as for the primary endpoint was also performed.

A sensitivity analysis for the change from Baseline in MG-ADL total score at Week 26 was performed, using a restricted maximum likelihood-based Repeated-Measures model that included the fixed categorical effects of treatment, visit, the treatment by visit interaction, and the pooled randomization stratification variable, as well as the continuous fixed covariate of the Baseline MG-ADL total score with an unstructured (co)variance structure used to model the within-patient errors.

Sensitivity analyses for the change from Baseline in QMG, MGC, and MG-QoL15 total score at Week 26 were also performed using a Repeated-Measures model, with effects for treatment and visit, as described for the primary endpoint.

Another sensitivity analysis for the actual change from Baseline in the MG-ADL total score at Week 26 was also performed. In this sensitivity analysis, treatment arms were compared using a Repeated-Measures model with effects for treatment, visit, and the treatment by visit interaction. The Baseline MG-ADL total score, the pooled randomization stratification variable, and an indicator for the IST treatment status of the patient (3 categories) were covariates in the model.

Subgroups Analyses: Subgroup analyses were planned to investigate the effect of randomization stratification variable (MGFA clinical classification), age group (≤65 or >65 years), gender, race, region, MG-ADL total score groups (≤7, 8 to 9, 10 through 12, or 13 through 18), thymectomy (yes versus no), and rescue therapy (yes versus no) on the primary and secondary efficacy endpoints. In addition, the subgroup analyses were also performed toward to 2 subgroups of patients who failed ISTs. The following 2 subgroups were determined using the MGFA MG therapy status at the Screening visit:
1. Patients who failed treatment over ≥1 year with ≥2 ISTs in sequence or in combination. This was determined using the MGFA MG therapy status at the Screening Visit based on patients who did not require chronic PE and who did not require chronic IVIg.
2. Patients who failed ≥1 IST and required chronic PE or chronic IVIg to control symptoms. This was determined using the MGFA MG therapy status at the Screening Visit based on patients who required chronic PE and/or chronic IVIg.

Changes in the Conduct of the Study or Planned Analyses:
The original protocol, dated 15 Aug 2013, was globally amended once during the study. This clinical study report is written based on the information in Protocol Version 2.0, dated

13 Jun 2014. Three administrative letters and 2 country-specific amendments were also submitted and are described. 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. Specific records in the clinical database were unlocked for a total of 7 patients to address the identified inconsistencies.
Very few patients entered the study with Baseline MGFA Classification of IVa or IVb. 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.

In addition, additional changes occurred after SAP Version 3.0 was finalized. However, these changes are considered exploratory in nature.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.1.3.1 Patient Disposition

A total of 170 subjects were screened, of whom 126 were enrolled into the study and were randomized. A total of 125 were treated and 1 patient (Patient (b) (6)) was randomized to the Eculizumab arm in error and never received study drug. Of the 125 treated patients, 62 were randomized to the Eculizumab arm and 63 were randomized to the placebo arm. Of these subjects, a total of 8 (6.3%) subjects discontinued from the study and 118 (93.7%) subjects were considered completed the study: 61 (96.8%) in placebo; 57 (90.5%) in Eculizumab. One patient randomized to the Eculizumab arm (Patient (b) (6)) was unblinded by the Investigator during the study due to MG crisis; however, Alexion remained blinded. Overall, subject disposition was similar across the two treatment groups.

Eight subjects were discontinued for the reasons shown in Table 3-2 and Table 3-3.

Table 3-2 Patient Disposition (All Randomized Patients)

Status	Placebo n (%)	Eculizumab n (%)	Total N (%)
Randomized	63 (100.0)	63 (100.0)	126 (100.0)
Treated	63 (100.0)	62 (98.4)	125 (99.2)
Completed the Study	61 (96.8)	57 (90.5)	118 (93.7)
Discontinued	2 (3.2)	6 (9.5)	8 (6.3)
Adverse Event	0 (0.0)	4 (6.3)	4 (3.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by Patient	2 (3.2)	1 (1.6)	3 (2.4)
Other	0 (0.0)	1 (1.6)	1 (0.8)
Enrolled in Open-Label Extension Study (Study ECU-MG-302)	61 (96.8)	56 (88.9)	117 (92.9)

[Source: Sponsor]

Table 3-3 Clinical Deterioration and Rescue Therapy

Variable	Statistic	Eculizumab (N=62)	Placebo (N=63)
Total number of patients reporting clinical deterioration	n (%)	6 (9.7)	11 (17.5)
Total number of patients requiring rescue therapy	n (%)	6 (9.7)	12 (19.0)

[Source: Reviewer]

The number of subjects for each analysis set was summarized in Table 3-4.

Table 3-4 Summary of Analysis Population

Analyzed populations	Placebo n (%)	Eculizumab n (%)
Full Analysis Set (FAS)	63 (100%)	62 (100%)
Per Protocol (PP) Set	56 (88.9%)	54 (87.1%)

[Source: Reviewer]

Fifteen patients from the FAS were not included in the PP Set, including 7 patients from the placebo arm and 8 patients from the Eculizumab arm as in Table 3-4. The most common reason for exclusion from the PP Set is not having a stable dose of IST therapy at the time of enrollment and/or having a change in IST status during the study (5 patients from the placebo arm and 7 patients from the Eculizumab arm). One patient in the placebo arm (Patient (b) (6)) was excluded from the PP Set because he had an MG-ADL assessment performed by himself instead of by a trained evaluator. Another patient from the placebo arm (Patient (b) (6)) was excluded from the PP Set because his compliance with the study drug was <80%. One patient (Patient (b) (6)) from the Eculizumab arm was excluded from the PP Set because she required emergency unblinding during the study.

3.2.1.3.2 Demographic and Baseline Characteristics

The reviewer can regenerate the summary results on demographic and baseline characteristics for the efficacy analysis population except for the variable Age at First IP Dose (years) as shown in Table 3-5.

Table 3-5 Demographics and Physics Characteristics (FAS Population)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Total (N = 125)
Age at First IP Dose (years) (1)	**n**	**6**	**6**	**1**
	Mean	**46.9 (17.98)**	**47.5 (15.66)**	**47.2 (16.80)**
	Median	**4**	**44.5**	**4**
	Min,	**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**	**6**	**6**	**1**
	Mean	**86.24**	**87.67**	**86.95**
	Median	**83.**	**80.**	**80.**
	Min,	**37.0, 155.5**	**42.9, 173.6**	**37.0, 173.6**
Height (cm)	**n**	**6**	**6**	**1**
	Mean	**167.07**	**166.63**	**166.85**
	Median	**167.50**	**165.10**	**166.70**
	Min,	**139.7, 184.2**	**150.1, 186.2**	**139.7, 186.2**
BMI (kg/m^2) (2)	**n**	**6**	**6**	**1**
	Mean	**30.53 (8.373)**	**31.37 (8.997)**	**30.94 (8.663)**
	Median	**30.**	**30.**	**30.**
	Min,	**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)**
[Source: Sponsor Page 83 of the final study report]				

3.2.1.4 Results and Conclusions

3.2.1.4.1 Sponsor's Analyses

Primary Efficacy Endpoint: change from Baseline in MG-ADL total score at Week 26

For the pre-specified primary MG-ADL Worst-Rank ANCOVA as described in the SAP Version 3, the least square mean changes in rank of MG-ADL score from baseline to Week 26 were 68.3 in the placebo group (N=63), 56.6 in the Eculizumab group (p=0.0698 versus placebo).

Table 3-6 Change from Baseline in Myasthenia Gravis Activities of Daily Living Total Score at Week 26: (ANCOVA Worst –Rank Analysis; FAS; SAP V3.0)

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)	

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.
[Source: Sponsor]

Following the SAP Version 3, three clinically improved but discontinued patients were placed in the clinically deteriorated rescue cohort. These patients in the Eculizumab arm discontinued due to an AE, were not identified by the physician as in need of rescue therapy, did not receive rescue therapy, and did not fulfill the pre-specified clinical deterioration criteria sufficient for rescue therapy. Indeed, each of these 3 discontinued patients individually fulfilled the pre-specified criteria for significant clinical improvement. The sponsor re-analyzed the data following the SAP Version 2. The results are summarized in Table 3-5.

Table 3-7 Change from Baseline in Myasthenia Gravis Activities of Daily Living Total Score at Week 26: (ANCOVA Worst –Rank Analysis; FAS; SAP V2.0)

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)	70.2(4.41)	54.8(4.46)	-15.4	0.0160
	95% CI for LS Mean	(61.41, 78.89)	(45.97, 63.63)	(-27.80, -2.92)	
Note: p-value from worst rank ANCOVA model to test whether treatment groups 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 with worst ranks based on time to death, time to MG crisis, time to Drop-out due to ADL Worsening, time to rescue therapy, and finally change in MG-ADL at Week 26 or LOCF with greatest improvement getting the rank of 1					

[Source: Sponsor]

Secondary Efficacy Analysis

The sponsor analyzed the following secondary endpoints.

- 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 Myasthenia Gravis Quality of Life 15-item Scale (MG-QoL15) at Week 26

Table 3-8 Change from Baseline in QMG Total Score at Week 26: ANCOVA Worst Ranked Score Analysis (SAP3; FAS)

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)	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)	
Note: p-value from worst rank ANCOVA model to test whether treatment groups are equal. The worst rank model includes the following terms: treatment, the pooled MGFA randomization stratification variable, and score at baseline. Patients are ranked with worst ranks based on t ime to death, time to MG Crisis, time to rescue therapy, and then change from baseline at Week 26 or LOCF with greatest improvement getting the rank of 1.					

[Source: Sponsor]

Table 3-9 Proportion of Subjects with at Least a 3-point Reduction in MG-ADL Total Score from Baseline to Week 26 and No Rescue Therapy (CMH test; FAS)

	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.					

[Source: Sponsor]

Table 3-10 Proportion of Subjects with at Least a 5-point Reduction in QMG Total Score from Baseline to Week 26 and No Rescue Therapy by Treatment Group (CMH Test; FAS)

	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.					

[Source: Sponsor]

Table 3-11 Change from Baseline in MGC Scale Total Score at Week 26: ANCOVA Worst Ranked Score Analysis (SAP3; FAS)

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)	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)	

Note: p-value from worst rank ANCOVA model to test whether treatment groups 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 drop-out, and finally change in MGC at Week 26 or LOCF with greatest improvement getting the rank of 1.

[Source: Sponsor]

Table 3-12 Change from Baseline in MG-QOL15 Total Score at Week 26: ANCOVA Worst Ranked Score Analysis (SAP3; FAS)

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)	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)	

Note: p-value from worst rank ANCOVA model to test whether treatment groups 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 drop-out, and finally change in MG-QOL15 at Week 26 or LOCF with greatest improvement getting the rank of 1.

[Source: Sponsor]

Table 3-13 Time from Baseline to a 3-point Reduction in MG-ADL Total Score by Treatment (Cox Regression; FAS; with rescue therapy)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)
Time from Baseline to a 3-Point Reduction in MG-ADL Total Score (days)	Median (1)	54.0	15.5
	95% CI (2)	(22.0, 71.0)	(9.0, 57.0)
	p-value (3)		0.3207

Note: For patients with rescue therapy, MG-ADL assessments after rescue therapy were also included in analysis. Patients who did not achieve a 3-point or more reduction in MG-ADL Total Score were censored at date of study completion or discontinuation.
(1) Kaplan-Meier estimate of the median.
(2) Brookmeyer-Crowley CI for the median.
(3) p-value from Wald chi-square test for a difference between treatments from a Cox proportional hazards regression model with terms for treatment and the pooled MGFA randomization stratification group.

[Source: Sponsor]

Table 3-14 Time from Baseline to a 3-point Reduction in MG-ADL Total Score by Treatment Group (Cox Regression; FAS; without rescue therapy)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)
Time from Baseline to a 3-Point Reduction in MG-ADL Total Score (days)	Median (1)	54.0	15.0
	95% CI (2)	(22.0, 60.0)	(9.0, 55.0)
	p-value (3)		0.1842

Note: For patients with rescue therapy, MG-ADL assessments after rescue therapy were also included in analysis. Patients who did not achieve a 3-point or more reduction in MG-ADL Total Score were censored at date of study completion or discontinuation.
(1) Kaplan-Meier estimate of the median.
(2) Brookmeyer-Crowley CI for the median.
(3) p-value from Wald chi-square test for a difference between treatments from a Cox proportional hazards regression model with terms for treatment and the pooled MGFA randomization stratification group.

[Source: Sponsor]

3.2.1.4.2 Reviewer's Analyses

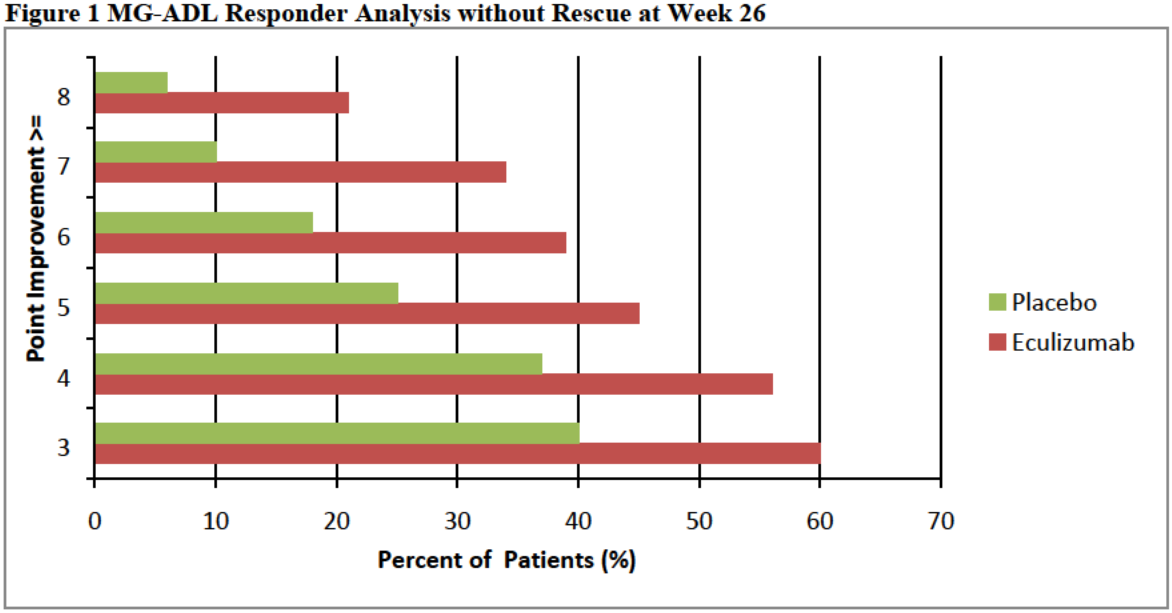
Primary Endpoint: change from Baseline in MG-ADL total score at Week 26

This reviewer can repeat the sponsor's primary efficacy analyses as reported in the FSR. The primary MG-ADL worst rank ANCOVA analysis was not statistically significant (p = 0.0698) based on SAP3 which assigns all discontinuations to the rescue cohort irrespective of clinically-validated MG outcomes. However, in this analysis three discontinued but clinically improved patients were assigned to the rescue group, which may not be sensible. During the Type C meeting dated 9/14/2016, the review team expressed understanding of the sponsor' rationale concerning the most appropriate interpretation of the study's findings. Thus, the worst rank analysis based on SAP2 was deemed clinically justifiable, which resulted in p = 0.0140 for this primary endpoint.

Secondary Endpoints:

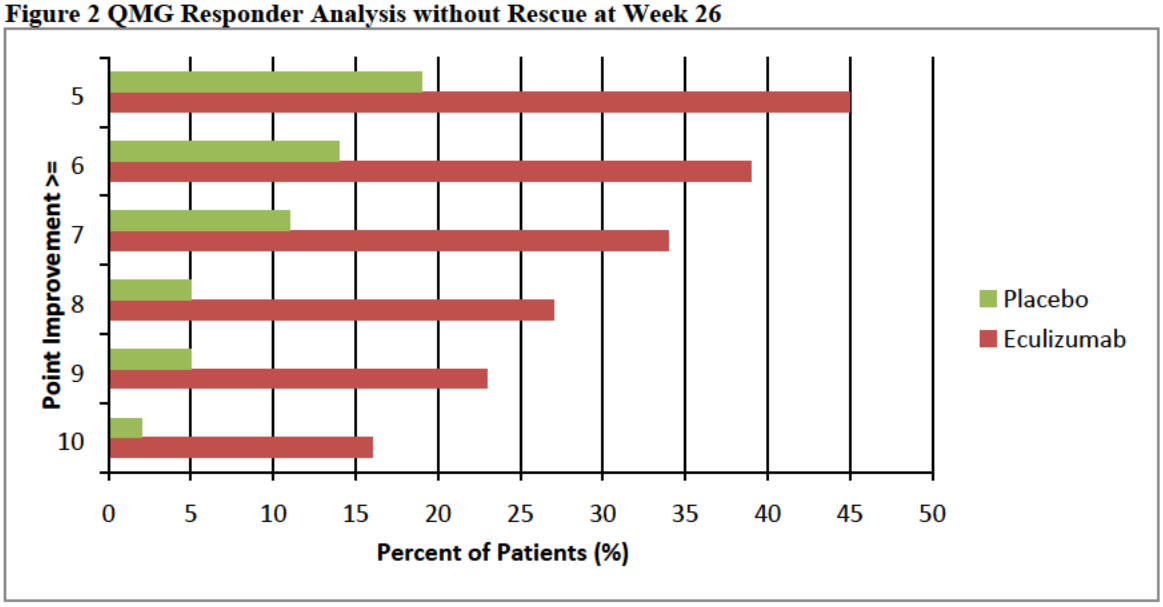
This reviewer can repeat the sponsor's secondary efficacy analyses as reported in the FSR. Following the SAP 2, the secondary endpoints QMG, MGC, and MG-QoL15 show significant treatment effects (p = 0.0129, p = 0.037 and p= 0.0119). At increasing thresholds for MG-ADL (i.e. ≥4, 5, 6, 7 or 8-point improvements in MG-ADL), the proportion of responders was consistently higher on Eculizumab versus placebo as shown in Figure 1.

Figure 1 MG-ADL Responder Analysis without Rescue at Week 26



At increasing thresholds for QMG (i.e. ≥6, 7, 8, 9 or 10-point improvements), the proportion of responders was consistently higher on Eculizumab versus placebo as shown in Figure 2.

Figure 2 QMG Responder Analysis without Rescue at Week 26



3.2.1.4.3 Sensitivity Analyses

The sponsor did the following sensitivity analyses for the primary endpoint.
The actual change from Baseline in the MG-ADL total score at Week 26 using the pre-specified ANCOVA analysis.

- The change from Baseline in MG-ADL total score at Week 26 and other study visits using a Repeated-Measures Analysis Model. Note that this sensitivity analysis includes the observations for patients after rescue.
- The change from Baseline in MG-ADL total score at Week 26 and other study visits, including IST treatment status as a covariate using a Repeated-Measures Analysis Model. Note that this sensitivity analysis includes the observations for patients after rescue.
- The change from Baseline in the MG-ADL total score at Week 26 using the Worst-Rank ANCOVA with patients in Rescue Cohort (including all discontinuations) ranked using the actual changes from Baseline (LOCF)

The results are shown as follows.

Table 3-15 Change from Baseline in MG-ADL Total Score at Week 26: (ANCOVA; FAS)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Change from Baseline (1)	LS Mean (SEM)	-2.6 (0.48)	-4.0 (0.48)	-1.4	0.0390
	95% CI for LS Mean	(-3.52, -1.63)	(-4.96, -3.04)	(-2.77, -0.07)	
Baseline MG-ADL Total Score	n	63	62		
	Mean (SD)	9.9 (2.58)	10.5 (3.06)		
	Median	9.0	10.0		
	Min, Max	5, 18	5, 18		
Week 26 MG-ADL Total Score (LOCF)	n	63	62		
	Mean (SD)	7.4 (3.50)	6.4 (4.76)		
	Median	7.0	6.0		
	Min, Max	0, 16	0, 17		
Change from Baseline to Week 26 in MG-ADL Total Score	n	63	62		
	Mean (SD)	-2.4 (3.32)	-4.1 (4.48)		
	Median	-2.0	-4.0		
	Min, Max	-8, 7	-15, 4		

(1) LS Means are from the ANCOVA model.
Note: p-value from ANCOVA analysis of change from baseline, testing for the effect of treatment, with the baseline value and the pooled MGFA randomization stratification variable as covariates in the model. For patients who did not require rescue therapy, if the Week 26 MG-ADL total score was missing or an item from the Week 26 MG-ADL was missing, last observation carried forward (LOCF) was used for missing Week 26 MG-ADL total score or missing item was missing or an item from the Week 26 MG-ADL was missing, last observation carried forward (LOCF) was used for missing Week 26 MG-ADL total score or missing item of the Week 26 MG-ADL. For patients requiring rescue therapy, the last observation prior to the first use of rescue therapy was used. If the last observation prior to the first use of rescue therapy was missing an item from the MG-ADL, last observation carried forward was used for the missing item.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Max = maximum; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; MGFA = Myasthenia Gravis Foundation of America; Min = minimum; SD = standard deviation; SEM = standard error of the mean.

[Source: Sponsor]

Table 3-16 Change from Baseline in MG-ADL Total Score at Week 26 and Other Study Visits (RMM; FAS)

Variable		Statistic	Placebo (N=63)	Eculisumab (N=62)	Difference in LS Means and 95% CI	p-value
Week	1	n	62	62		0.0125
		LS Means (SEM)	-0.9 (0.28)	-1.9 (0.28)	-1.0	
		95% CI for LS Mean	(-1.5, -0.3)	(-2.5, -1.4)	(-1.8, -0.2)	
Week	2	n	63	62		0.0002
		LS Means (SEM)	-0.9 (0.36)	-2.9 (0.37)	-2.0	
		95% CI for LS Mean	(-1.6, -0.2)	(-3.7, -2.2)	(-3.0, -1.0)	
Week	3	n	63	62		0.0505
		LS Means (SEM)	-1.8 (0.39)	-2.9 (0.40)	-1.1	
		95% CI for LS Mean	(-2.6, -1.0)	(-3.7, -2.1)	(-2.2, 0.0)	
Week	4	n	62	61		0.0008
		LS Means (SEM)	-1.5 (0.41)	-3.5 (0.41)	-2.0	
		95% CI for LS Mean	(-2.3, -0.7)	(-4.3, -2.7)	(-3.2, -0.9)	
Week	8	n	62	58		0.0046
		LS Means (SEM)	-1.8 (0.47)	-3.7 (0.48)	-1.9	
		95% CI for LS Mean	(-2.7, -0.8)	(-4.6, -2.7)	(-3.3, -0.6)	
Week	12	n	61	58		0.0183
		LS Means (SEM)	-2.1 (0.47)	-3.7 (0.47)	-1.6	
		95% CI for LS Mean	(-3.1, -1.2)	(-4.7, -2.8)	(-2.9, -0.3)	
Week	16	n	60	58		0.0096
		LS Means (SEM)	-2.6 (0.47)	-4.4 (0.48)	-1.8	
		95% CI for LS Mean	(-3.6, -1.7)	(-5.3, -3.5)	(-3.1, -0.4)	
Week	20	n	61	57		0.0107
		LS Means (SEM)	-2.5 (0.48)	-4.3 (0.49)	-1.8	
		95% CI for LS Mean	(-3.4, -1.5)	(-5.2, -3.3)	(-3.2, -0.4)	
Week	26	n	60	57		0.0058
		LS Means (SEM)	-2.3 (0.48)	-4.2 (0.49)	-1.9	
		95% CI for LS Mean	(-3.2, -1.4)	(-5.2, -3.3)	(-3.3, -0.6)	

Note: p-value from a restricted maximum likelihood (REML) based repeated-measures analysis of change from baseline, testing whether the LS Means for the two treatments are equal.
The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, and the MG-ADL total score at baseline. Missing MG-ADL total score values were not imputed.

[Source: Sponsor]

Table 3-17 Change from Baseline in MG-ADL Total Score at Week 26 and Other Study Visits: (RMM; FAS; IST)

Variable		Statistic	Placebo (N=63)	Eculisumab (N=62)	Difference in LS Means and 95% CI	p-value
Week	1	n	62	62		0.0221
		LS Means (SEM)	-0.9 (0.31)	-1.8 (0.32)	-0.9	
		95% CI for LS Mean	(-1.5, -0.3)	(-2.5, -1.2)	(-1.7, -0.1)	
Week	2	n	63	62		0.0003
		LS Means (SEM)	-0.9 (0.38)	-2.8 (0.39)	-1.9	
		95% CI for LS Mean	(-1.7, -0.2)	(-3.6, -2.1)	(-2.9, -0.9)	
Week	3	n	63	62		0.0702
		LS Means (SEM)	-1.8 (0.41)	-2.8 (0.42)	-1.0	
		95% CI for LS Mean	(-2.6, -1.0)	(-3.6, -2.0)	(-2.1, 0.1)	
Week	4	n	62	61		0.0013
		LS Means (SEM)	-1.5 (0.43)	-3.4 (0.44)	-1.9	
		95% CI for LS Mean	(-2.3, -0.6)	(-4.3, -2.5)	(-3.1, -0.8)	
Week	8	n	62	58		0.0060
		LS Means (SEM)	-1.7 (0.48)	-3.6 (0.49)	-1.8	
		95% CI for LS Mean	(-2.7, -0.8)	(-4.6, -2.6)	(-3.2, -0.5)	
Week	12	n	61	58		0.0242
		LS Means (SEM)	-2.1 (0.48)	-3.6 (0.49)	-1.5	
		95% CI for LS Mean	(-3.1, -1.2)	(-4.6, -2.7)	(-2.8, -0.2)	
Week	16	n	60	58		0.0130
		LS Means (SEM)	-2.6 (0.48)	-4.3 (0.49)	-1.7	
		95% CI for LS Mean	(-3.6, -1.7)	(-5.3, -3.3)	(-3.0, -0.4)	
Week	20	n	61	57		0.0141
		LS Means (SEM)	-2.5 (0.50)	-4.2 (0.51)	-1.7	
		95% CI for LS Mean	(-3.4, -1.5)	(-5.2, -3.2)	(-3.1, -0.4)	
Week	26	n	60	57		0.0077
		LS Means (SEM)	-2.3 (0.49)	-4.1 (0.50)	-1.8	
		95% CI for LS Mean	(-3.2, -1.4)	(-5.2, -3.3)	(-3.3, -0.6)	

Note: p-value from a restricted maximum likelihood (REML) based repeated-measures analysis of change from baseline, testing whether the LS Means for the two treatments are equal.
The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, and the MG-ADL total score at baseline. Missing MG-ADL total score values were not imputed.

[Source: Sponsor]

Table 3-18 Change from Baseline in MG-Total Score at Week 26: (ANCOVA; Worst Rank; FAS)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Worst Ranked Change from Baseline	Ranked Score LS Mean (SEM)	68.1 (4.48)	56.8 (4.53)	-11.3	0.0800
	95% CI for LS Mean	(59.23, 76.97)	(47.87, 65.80)	(-23.89, 1.37)	
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 groups are equal. The worst rank model includes the following te rms: treatment, the pooled MGFA randomization stratification variable, and MG-ADL total score at baseline. Patients are ranked according to change in MG-ADL with worst ranks based on death, MG Crisis, rescue therapy or drop -out, and finally change in MG-ADL at Week 26 or LOCF with greatest improvement getting the rank of 1.

[Source: Sponsor]

This reviewer did additional sensitivity analyses to address the concerns raised by the changes to the database during the database unlock. Per the rationales listed in Table 3-1, the changes that were made to Subject (b) (6) and Subject (b) (6) could potentially impact the inference on treatment effect. For scenario I, the data for these two subjects are considered non-reliable and should be removed from the analysis population; for scenario II, these two subjects are completers without any rescue. The analysis results in Table 3-18 show that the estimated treatment effects in both scenarios are reduced relative to the original analyses (Tables 3-5 and 3-6) and the corresponding p-values increase. Nonetheless, statistical significance remains for both scenarios following the SAP2.

Table 3-19 Additional Sensitivity Analysis in MG-Total Score.

Scenario	Variable	Statistic	Placebo	Eculizumab	Difference in LS Means and 95% CI	p-value
I:FAS without both subjects (SAP3)	Worst Ranked Change from Baseline	n	61	62		
		LSM (SEM)	66.9 (4.5)	56.6 (4.5)	-10.3(6.4)	0.1097
		95% CI for LEM	(58.0, 75.9)	(47.7, 65.5)	(-23.0, 2.4)	
I:FAS without both subjects (SAP2)	Worst Ranked Change from Baseline	n	61	62		
		LSM (SEM)	69.0 (4.5)	54.6 (4.4)	-14.3 (6.3)	0.0245
		95% CI for LEM	(60.1, 45.8)	(45.8, 63.4)	(-26.8, -1.9)	
II:FAS (SAP3)	Worst Ranked Change from Baseline	n	63	62		
		LSM (SEM)	67.8 (4.5)	57.3 (4.6)	-10.5 (6.4)	0.1050
		95% CI for LEM	(58.8, 76.7)	(48.3, 66.3)	(-23.2, 2.2)	
II:FAS (SAP2)	Worst Ranked Change from Baseline	n	63	62		
		LSM (SEM)	69.8 (4.4)	55.2 (4.5)	-14.6 (6.3)	0.0228
		95% CI for LEM	(61.0, 78.6)	(46.4, 64.1)	(-27.1, -2.1)	

[Source: Reviewer]

Table 3-20 Sensitivity Analysis in QMG Score.

Scenario	Variable	Statistic	Placebo	Eculizumab	Difference in LS Means and 95% CI	p-value
Original (SAP2)	Worst Ranked Change from Baseline	n	63	62		
		LSM (SEM)	71.7 (4.4)	53.7 (4.5)	-18.0 (-30.4, -5.6)	0.0047
		95% CI for LEM	(63.0, 80.5)	(44.9, 62.5)		
I:FAS without both subjects (SAP3)	Worst Ranked Change from Baseline	n	61	62		
		LSM (SEM)	69.2 (4.5)	54.8 (4.5)	-14.4(6.3)	0.0247
		95% CI for LEM	(60.3, 75.9)	(45.9, 65.5)	(-27.0, -1.9)	
I:FAS without both subjects (SAP2)	Worst Ranked Change from Baseline	n	61	62		
		LSM (SEM)	70.3 (4.4)	53.8 (4.4)	-16.5 (6.3)	0.0097
		95% CI for LEM	(61.5, 79.0)	(45.0, 62.6)	(-28.8, -4.1)	
II:FAS (SAP3)	Worst Ranked Change from Baseline	n	63	62		
		LSM (SEM)	70.3 (4.5)	55.2 (4.5)	-15.1 (6.3)	0.0187
		95% CI for LEM	(61.5, 79.2)	(46.2, 64.1)	(-27.7, -2.6)	
II:FAS (SAP2)	Worst Ranked Change from Baseline	n	63	62		
		LSM (SEM)	71.4 (4.4)	54.1 (4.5)	-17.3 (6.3)	0.0068
		95% CI for LEM	(62.7, 80.2)	(45.3, 63.0)	(-29.7, -4.9)	

[Source: Reviewer]

Table 3-21 Sensitivity Analysis in MGC Score.

Scenario	Variable	Statistic	Placebo	Eculizumab	Difference in LS Means and 95% CI	p-value
Original (SAP2)	Worst Ranked Change from Baseline	n	63	62		
		LSM (SEM)	69.1 (4.4)	55.9 (4.4)	-13.2 (-25.6, -0.8)	0.0371
		95% CI for LEM	(60.4, 77.8)	(47.1, 64.7)		
I:FAS without both subjects (SAP3)	Worst Ranked Change from Baseline	n	61	62		
		LSM (SEM)	66.4 (4.5)	57.1 (4.5)	-9.3(6.4)	0.1483
		95% CI for LEM	(57.5, 75.4)	(48.2, 66.0)	(-21.9, 3.4)	
I:FAS without both subjects (SAP2)	Worst Ranked Change from Baseline	n	61	62		
		LSM (SEM)	67.9 (4.4)	55.8 (4.4)	-14.3 (6.3)	0.0569
		95% CI for LEM	(59.0, 76.7)	(47.0, 64.5)	(-24.5, 0.4)	
II:FAS (SAP3)	Worst Ranked Change from Baseline	n	63	62		
		LSM (SEM)	67.2 (4.5)	57.8 (4.5)	-9.4 (6.4)	0.1439
		95% CI for LEM	(58.3, 76.1)	(48.8, 66.8)	(-22.1, 3.3)	
II:FAS (SAP2)	Worst Ranked Change from Baseline	n	63	62		
		LSM (SEM)	68.7 (4.4)	56.4 (4.5)	-12.2 (6.3)	0.0547
		95% CI for LEM	(59.9, 77.4)	(47.6, 65.3)	(-24.7, 0.24)	

[Source: Reviewer]

Table 3-22 Sensitivity Analysis in MG-QoL15 Score.

Scenario	Variable	Statistic	Placebo	Eculizumab	Difference in LS Means and 95% CI	p-value
Original (SAP2)	Worst Ranked Change from Baseline	n	63	62		
		LSM (SEM)	70.7 (4.5)	54.4 (4.5)	-16.3 (-28.9, -3.7)	0.0119
		95% CI for LEM	(61.8, 79.5)	(45.5, 63.4)		
I:FAS without both subjects (SAP3)	Worst Ranked Change from Baseline	n	61	62		
		LSM (SEM)	68.2 (4.5)	55.6 (4.5)	-12.7(6.4)	0.0512
		95% CI for LEM	(59.2, 77.3)	(46.6, 64.5)	(-25.4, 0.1)	
I:FAS without both subjects (SAP2)	Worst Ranked Change from Baseline	n	61	62		
		LSM (SEM)	69.2 (4.5)	54.5 (4.5)	-14.7 (6.4)	0.0232
		95% CI for LEM	(60.3, 78.2)	(45.6, 63.4)	(-27.3, -2.0)	
II:FAS (SAP3)	Worst Ranked Change from Baseline	n	63	62		
		LSM (SEM)	69.2 (4.5)	56.1 (4.6)	-13.1 (6.4)	0.0436
		95% CI for LEM	(60.2, 78.2)	(47.0, 65.1)	(-25.9, -0.4)	
II:FAS (SAP2)	Worst Ranked	n	63	62		
		LSM (SEM)	70.2 (4.5)	55.0 (4.5)	-15.2 (6.4)	0.0192

Scenario	Variable	Statistic	Placebo	Eculizumab	Difference in LS Means and 95% CI	p-value
	Change from Baseline	95% CI for LEM	(61.3, 79.1)	(46.0, 64.0)	(-27.8, -2.5)	

[Source: Reviewer]

The sponsor did the following sensitivity analyses for the change from Baseline in the QMG total score at Week 26.

- The change from Baseline in the QMG total score at Week 26 using the Worst-Rank ANCOVA with patients in Rescue Cohort (including all discontinuations) ranked using the actual changes from Baseline (LOCF)
- The change from Baseline in QMG total score at Week 26 and other study visits using a Repeated-Measures Analysis Model. Note that this sensitivity analysis includes the observations for patients after rescue.
- The change from Baseline in QMG total score at Week 26 and other study visits, including IST treatment status as a covariate using a Repeated-Measures Analysis Model. Note that this sensitivity analysis includes the observations for patients after rescue.
- The actual change from Baseline in the QMG total score at Week 26 using the pre-specified ANCOVA analysis.

Table 3-23 Change from Baseline in QMG Total Score at Week 26 (ANCOVA Worst Ranked Score Analysis; SAP3; FAS)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Change from Baseline (1)	LS Mean (SEM)	70.7 (4.46)	54.7 (4.50)	-	0.0129
	95% CI for LS Mean	(61.85, 79.51)	(45.82, 63.64)	(-28.48, -3.43)	
Note: p-value from worst rank ANCOVA model to test whether treatment groups are equal. The worst rank model includes the following te rms: 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 drop-out, and finally change in QMG at Week 26 or LOCF with greatest improvement getting the rank of 1.					

[Source: Sponsor]

Table 3-24 Change from Baseline in QMG Total Score at Week 26 and Other Study Visits: (RMM; actual changes; FAS)

Variable		Statistic	Placebo (N=63)	Eculisumab (N=62)	Difference in LS Means and 95% CI	p-value
Week	1	n	62	61		0.0644
		LS Means (SEM)	-0.9 (0.37)	-1.9 (0.37)	-1.0	
		95% CI for LS Mean	(-1.6, -0.1)	(-2.6, -1.1)	(-2.0, 0.1)	
Week	2	n	62	62		0.0071
		LS Means (SEM)	-1.0 (0.45)	-2.7 (0.45)	-1.7	
		95% CI for LS Mean	(-1.9, -0.1)	(-3.6, -1.8)	(-3.0, -0.5)	
Week	3	n	63	62		0.0472
		LS Means (SEM)	-1.5 (0.51)	-2.9 (0.51)	-1.4	
		95% CI for LS Mean	(-2.5, -0.5)	(-4.0, -1.9)	(-2.9, -0.0)	
Week	4	n	61	61		0.0256
		LS Means (SEM)	-1.5 (0.55)	-3.3 (0.55)	-1.8	
		95% CI for LS Mean	(-2.6, -0.4)	(-4.4, -2.2)	(-3.3, -0.2)	
Week	8	n	61	58		0.0021
		LS Means (SEM)	-1.4 (0.59)	-4.0 (0.60)	-2.7	
		95% CI for LS Mean	(-2.5, -0.2)	(-5.2, -2.8)	(-4.3, -1.0)	
Week	12	n	60	58		0.0053
		LS Means (SEM)	-1.6 (0.62)	-4.1 (0.63)	-2.5	
		95% CI for LS Mean	(-2.8, -0.4)	(-5.4, -2.9)	(-4.3, -0.8)	
Week	16	n	60	58		0.0056
		LS Means (SEM)	-1.9 (0.56)	-4.2 (0.57)	-2.3	
		95% CI for LS Mean	(-3.0, -0.8)	(-5.3, -3.0)	(-3.8, -0.7)	
Week	20	n	60	57		0.0022
		LS Means (SEM)	-1.4 (0.59)	-4.0 (0.60)	-2.6	
		95% CI for LS Mean	(-2.6, -0.2)	(-5.2, -2.8)	(-4.3, -1.0)	
Week	26	n	60	56		0.0006
		LS Means (SEM)	-1.6 (0.59)	-4.6 (0.60)	-3.0	
		95% CI for LS Mean	(-2.8, -0.5)	(-5.8, -3.4)	(-4.6, -1.3)	

Note: p-value from a restricted maximum likelihood (REML) based repeated-measures analysis of change from baseline, testing whether the LS Means for the two treatments are equal.
The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, and the QMG total score at baseline.
Missing QMG total score values were not imputed.

[Source: Sponsor]

Table 3-25 Change from Baseline in QMG Total Score at Week 26 and Other Study Visits: (RMM; Actual changes; Including IST treatment status; FAS)

Variable		Statistic	Placebo (N=63)	Eculisumab (N=62)	Difference in LS Means and 95% CI	p-value
Week	1	n	62	61		0.0846
		LS Means (SEM)	-1.0 (0.41)	-1.9 (0.42)	-0.9	
		95% CI for LS Mean	(-1.8, -0.1)	(-2.7, -1.1)	(-2.0, 0.1)	
Week	2	n	62	62		0.0094
		LS Means (SEM)	-1.0 (0.48)	-2.7 (0.49)	-1.7	
		95% CI for LS Mean	(-2.0, -0.1)	(-3.7, -1.8)	(-3.0, -0.4)	
Week	3	n	63	62		0.0563
		LS Means (SEM)	-1.6 (0.53)	-3.0 (0.54)	-1.4	
		95% CI for LS Mean	(-2.6, -0.5)	(-4.0, -1.9)	(-2.8, 0.0)	
Week	4	n	61	61		0.0318
		LS Means (SEM)	-1.6 (0.58)	-3.3 (0.58)	-1.7	
		95% CI for LS Mean	(-2.7, -0.4)	(-4.4, -2.1)	(-3.3, -0.2)	
Week	8	n	61	58		0.0026
		LS Means (SEM)	-1.4 (0.62)	-4.1 (0.63)	-2.6	
		95% CI for LS Mean	(-2.7, -0.2)	(-5.3, -2.8)	(-4.3, -0.9)	
Week	12	n	60	58		0.0063
		LS Means (SEM)	-1.7 (0.64)	-4.1 (0.65)	-2.5	
		95% CI for LS Mean	(-3.0, -0.4)	(-5.4, -2.8)	(-4.2, -0.7)	
Week	16	n	60	58		0.0067
		LS Means (SEM)	-2.0 (0.58)	-4.2 (0.59)	-2.2	
		95% CI for LS Mean	(-3.1, -0.8)	(-5.4, -3.0)	(-3.8, -0.6)	
Week	20	n	60	57		0.0026
		LS Means (SEM)	-1.5 (0.61)	-4.1 (0.63)	-2.6	
		95% CI for LS Mean	(-2.7, -0.3)	(-5.3, -2.8)	(-4.3, -0.9)	
Week	26	n	60	56		0.0007
		LS Means (SEM)	-1.7 (0.61)	-4.6 (0.62)	-2.9	
		95% CI for LS Mean	(-2.9, -0.5)	(-5.8, -3.4)	(-4.6, -1.2)	

Note: p-value from a restricted maximum likelihood (REML) based repeated-measures analysis of change from baseline, testing whether the LS Means for the two treatments are equal.
The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, the QMG total score at baseline, and IST treatment status.
Missing values were not imputed.

[Source: Sponsor]

Table 3-26 Change from Baseline in QMG Total Score at Week 26 (ANCOVA; FAS)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Change from Baseline (1)	LS Mean (SEM)	-1.6 (0.59)	-4.2 (0.60)	-2.5	0.0032
	95% CI for LS Mean	(-2.82, -0.47)	(-5.37, -3.00)	(-4.21, -0.87)	
Baseline QMG Total Score	n	63	62		
	Mean (SD)	16.9 (5.56)	17.3 (5.10)		
	Median	16.0	17.0		
	Min, Max	8, 34	6, 31		
Week 26 QMG Total Score (LOCF)	n	63	62		
	Mean (SD)	15.3 (6.17)	13.1 (6.54)		
	Median	14.0	13.0		
	Min, Max	5, 32	1, 30		
Change from Baseline to Week 26 in QMG Total Score	n	63	62		
	Mean (SD)	-1.6 (4.21)	-4.2 (5.35)		
	Median	-2.0	-3.5		
	Min, Max	-11, 9	-16, 7		

(1) LS Means are from the ANCOVA model.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Max = maximum; Min = minimum; QMG = Quantitative Myasthenia Gravis score for disease severity; SD = standard deviation; SEM = standard error of the mean.
Note: p-value from ANCOVA analysis of change from baseline, testing for the effect of treatment, with the baseline value and the pool ed MGFA randomization stratification variable as covariates in the model. For patients who did not require rescue therapy, if the Week 26 QMG total score was missing or an item from the Week 26 QMG was missing, last observation carried forward (LOCF) was used for missing Week 26 QMG total score or missing item of the Week 26 QMG. For patients requiring rescue therapy, the last observation prior to the first use of rescue therapy was used. If the last ob servation prior to the first use of rescue therapy was missing an item from the QMG, last observation carried forward was used for the missing item

[Source: Sponsor]

The sponsor did the following sensitivity analyses for the change from Baseline in the MGC total score at Week 26.

- The change from Baseline in the MGC total score at Week 26 using the Worst-Rank ANCOVA with patients in Rescue Cohort (including all discontinuations) ranked using the actual changes from Baseline (LOCF)
- The change from Baseline in MGC total score at Week 26 and other study visits using a Repeated-Measures Analysis Model. Note that this sensitivity analysis includes the observations for patients after rescue.
- The change from Baseline in MGC total score at Week 26 and other study visits, including IST treatment status as a covariate using a Repeated-Measures Analysis Model. Note that this sensitivity analysis includes the observations for patients after rescue.
- The actual change from Baseline in the MGC total score at Week 26 using the pre-specified ANCOVA analysis.

Table 3-27 Change from Baseline in MGC Total Score at Week 26 (ANCOVA Worst Ranked Score Analysis; SAP3; FAS)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Worst Ranked Change	Ranked Score LS	67.6	57.3	-10.3	0.1084
	95% CI for LS	(58.78,	(48.39,	(-22.87, 2.31)	

Note: p-value from worst rank ANCOVA model to test whether treatment groups are equal. The worst rank model includes the following te rms: treatment, the pooled MGFA randomization stratification variable, and MGC total score at baseline.
Patients are ranked according to change in MGC with worst ranks based on death, MG Crisis, rescue therapy or drop-out, and finally change in MGC at Week
26 or LOCF with greatest improvement getting the rank of 1.

[Source: Sponsor]

Table 3-28 Change from Baseline in MGC Total Score at Week 26 and Other Study Visits (RMM; Actual Changes; FAS)

Variable		Statistic	Placebo (N=63)	Eculisumab (N=62)	Difference in LS Means and 95% CI	p-value
Week	1	n	62	61		0.0166
		LS Means (SEM)	-2.1 (0.50)	-3.8 (0.51)	-1.7	
		95% CI for LS Mean	(-3.1, -1.1)	(-4.8, -2.8)	(-3.2, -0.3)	
Week	2	n	63	62		<0.0001
		LS Means (SEM)	-2.0 (0.63)	-6.2 (0.63)	-4.2	
		95% CI for LS Mean	(-3.2, -0.7)	(-7.4, -4.9)	(-6.0, -2.4)	
Week	3	n	63	62		0.0076
		LS Means (SEM)	-3.4 (0.74)	-6.3 (0.74)	-2.8	
		95% CI for LS Mean	(-4.9, -2.0)	(-7.8, -4.8)	(-4.9, -0.8)	
Week	4	n	62	61		0.0007
		LS Means (SEM)	-3.5 (0.77)	-7.3 (0.77)	-3.8	
		95% CI for LS Mean	(-5.0, -2.0)	(-8.8, -5.8)	(-5.9, -1.6)	
Week	8	n	62	58		0.0003
		LS Means (SEM)	-3.5 (0.86)	-8.1 (0.88)	-4.6	
		95% CI for LS Mean	(-5.2, -1.8)	(-9.9, -6.4)	(-7.1, -2.2)	
Week	12	n	61	58		0.0324
		LS Means (SEM)	-4.6 (0.91)	-7.4 (0.93)	-2.8	
		95% CI for LS Mean	(-6.4, -2.8)	(-9.3, -5.6)	(-5.4, -0.2)	
Week	16	n	60	58		0.0108
		LS Means (SEM)	-5.2 (0.88)	-8.4 (0.89)	-3.2	
		95% CI for LS Mean	(-6.9, -3.4)	(-10.2, -6.6)	(-5.7, -0.8)	
Week	20	n	61	57		0.0063
		LS Means (SEM)	-4.6 (0.94)	-8.4 (0.96)	-3.7	
		95% CI for LS Mean	(-6.5, -2.8)	(-10.3, -6.5)	(-6.4, -1.1)	
Week	26	n	60	57		0.0134
		LS Means (SEM)	-4.8 (0.94)	-8.1 (0.96)	-3.4	
		95% CI for LS Mean	(-6.6, -2.9)	(-10.0, -6.2)	(-6.0, -0.7)	

Note: p-value from a restricted maximum likelihood (REML) based repeated-measures analysis of change from baseline, testing whether the LS Means for the two treatments are equal.
The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, and the MGC total score at baseline.
Missing MGC total score values were not imputed.

[Source: Sponsor]

Table 3-29 Change from Baseline in MGC Total Score at Week 26 and Other Study Visits: (RMM; Actual changes; Including IST treatment status; FAS)

Variable		Statistic	Placebo (N=63)	Eculisumab (N=62)	Difference in LS Means and 95% CI	p-value
Week	1	n	62	61		0.0258
		LS Means (SEM)	-1.9 (0.55)	-3.6 (0.57)	-1.6	
		95% CI for LS Mean	(-3.0, -0.9)	(-4.7, -2.4)	(-3.1, -0.2)	
Week	2	n	63	62		<0.0001
		LS Means (SEM)	-1.8 (0.67)	-5.9 (0.68)	-4.1	
		95% CI for LS Mean	(-3.2, -0.5)	(-7.3, -4.6)	(-5.9, -2.3)	
Week	3	n	63	62		0.0100
		LS Means (SEM)	-3.3 (0.77)	-6.0 (0.78)	-2.7	
		95% CI for LS Mean	(-4.8, -1.8)	(-7.6, -4.5)	(-4.8, -0.7)	
Week	4	n	62	61		0.0011
		LS Means (SEM)	-3.4 (0.80)	-7.0 (0.82)	-3.7	
		95% CI for LS Mean	(-5.0, -1.8)	(-8.6, -5.4)	(-5.8, -1.5)	
Week	8	n	62	58		0.0004
		LS Means (SEM)	-3.4 (0.89)	-7.9 (0.91)	-4.5	
		95% CI for LS Mean	(-5.1, -1.6)	(-9.7, -6.1)	(-7.0, -2.1)	
Week	12	n	61	58		0.0396
		LS Means (SEM)	-4.5 (0.93)	-7.2 (0.96)	-2.7	
		95% CI for LS Mean	(-6.3, -2.6)	(-9.1, -5.3)	(-5.3, -0.1)	
Week	16	n	60	58		0.0138
		LS Means (SEM)	-5.0 (0.90)	-8.2 (0.92)	-3.1	
		95% CI for LS Mean	(-6.8, -3.2)	(-10.0, -6.3)	(-5.6, -0.6)	
Week	20	n	61	57		0.0077
		LS Means (SEM)	-4.5 (0.96)	-8.1 (0.99)	-3.6	
		95% CI for LS Mean	(-6.4, -2.6)	(-10.1, -6.2)	(-6.3, -1.0)	
Week	26	n	60	57		0.0168
		LS Means (SEM)	-4.6 (0.97)	-7.9 (0.99)	-3.3	
		95% CI for LS Mean	(-6.5, -2.7)	(-9.9, -5.9)	(-5.9, -0.6)	

Note: p-value from a restricted maximum likelihood (REML) based repeated-measures analysis of change from baseline, testing whether the LS Means for the two treatments are equal.
The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, the MGC total score at baseline, and IST treatment status.
Missing values were not imputed.

[Source: Sponsor]

Table 3-30 Change from Baseline in MGC Total Score at Week 26 (ANCOVA; FAS)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Change from Baseline (1)	LS Mean (SEM)	-5.0 (0.94)	-7.8 (0.95)	-2.8	0.0406
	95% CI for LS Mean	(-6.90, -3.17)	(-9.70, -5.93)	(-5.43, -0.12)	
Baseline MGC Total Score	n	63	62		
	Mean (SD)	18.9 (5.95)	20.4 (6.13)		
	Median	19.0	21.0		
	Min, Max	7, 40	7, 35		
Week 26 MGC Total Score (LOCF)	n	63	62		
	Mean (SD)	14.2 (7.79)	12.4 (9.00)		
	Median	13.0	11.0		
	Min, Max	3, 37	0, 36		
Change from Baseline to Week 26 in MGC Total Score	n	63	62		
	Mean (SD)	-4.7 (6.65)	-8.0 (8.70)		
	Median	-5.0	-8.0		
	Min, Max	-21, 13	-24, 17		

(1) LS Means are from the ANCOVA model.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Max = maximum; MGC = Myasthenia Gravis Composite score; Min = minimum; SD = standard deviation; SEM = standard error of the mean.
Note: p-value from ANCOVA analysis of change from baseline, testing for the effect of treatment, with the baseline value and the pool ed MGFA randomization stratification variable as covariates in the model. For patients who did not require rescue therapy, if the Week 26 MGC total score was missing or an item from the Week 26 MGC was missing, last observation carried forward (LOCF) was used for missing Week 26 MGC total score or missing item of the Week 26 MGC. For patients requiring rescue therapy, the last observation prior to the first use of rescue therapy was used. If the last observation prior to the first use of rescue therapy was missing an item from the MGC, last observation carried forward was used for the missing item.

[Source: Sponsor]

The sponsor did the following sensitivity analyses for the change from Baseline in the MG-QoL15 total score at Week 26.

- The change from Baseline in the MG-QoL15 total score at Week 26 using the Worst-Rank ANCOVA with patients in Rescue Cohort (including all discontinuations) ranked using the actual changes from Baseline (LOCF)
- The change from Baseline in MG-QoL15 total score at Week 26 and other study visits using a Repeated-Measures Analysis Model. Note that this sensitivity analysis includes the observations for patients after rescue.
- The change from Baseline in MG-QoL15 total score at Week 26 and other study visits, including IST treatment status as a covariate using a Repeated-Measures Analysis Model. Note that this sensitivity analysis includes the observations for patients after rescue.
- The actual change from Baseline in the MG-QoL15 total score at Week 26 using the pre-specified ANCOVA analysis.

Table 3-31 Change from Baseline in MG-QoL15 Total Score at Week 26 (ANCOVA Worst Ranked Score Analysis; SAP3; FAS)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Worst Ranked Change	Ranked Score LS	69.5	55.6	-13.9	0.0328
	95% CI for LS	(60.54,	(46.61,	(-26.56, -1.15)	

Note: p-value from worst rank ANCOVA model to test whether treatment groups are equal. The worst rank model includes the following te rms: treatment, the pooled MGFA randomization stratification variable, and MG-QOL15 total score at baseline. Patients are ranked according to change in MG-QOL15 with worst ranks based on death, MG Crisis, rescue therapy or drop-out, and finally change in MG-QOL15 at Week 26 or LOCF with greatest improvement getting the rank of 1.

[Source: Sponsor]

Table 3-32 Change from Baseline in MG-QoL15 Total Score at Week 26 and Other Study Visits (RMM; Actual Changes; FAS)

Variable		Statistic	Placebo (N=63)	Eculisumab (N=62)	Difference in LS Means and 95% CI	p-value
Week	4	n	61	61		0.0395
		LS Means (SEM)	-3.5 (1.23)	-7.1 (1.23)	-3.6	
		95% CI for LS Mean	(-5.9, -1.0)	(-9.5, -4.6)	(-7.1, -0.2)	
Week	8	n	62	57		0.0002
		LS Means (SEM)	-2.8 (1.33)	-10.1 (1.36)	-7.3	
		95% CI for LS Mean	(-5.4, -0.2)	(-12.8, -7.4)	(-11.1, -3.6)	
Week	12	n	61	57		0.0193
		LS Means (SEM)	-5.9 (1.50)	-11.0 (1.52)	-5.1	
		95% CI for LS Mean	(-8.9, -2.9)	(-14.0, -7.9)	(-9.3, -0.8)	
Week	16	n	60	58		0.0076
		LS Means (SEM)	-6.0 (1.51)	-11.8 (1.53)	-5.8	
		95% CI for LS Mean	(-9.0, -3.0)	(-14.8, -8.8)	(-10.1, -1.6)	
Week	20	n	61	57		0.0028
		LS Means (SEM)	-5.4 (1.49)	-11.9 (1.52)	-6.5	
		95% CI for LS Mean	(-8.4, -2.5)	(-14.9, -8.9)	(-10.7, -2.3)	
Week	26	n	60	57		0.0010
		LS Means (SEM)	-5.4 (1.49)	-12.6 (1.52)	-7.2	
		95% CI for LS Mean	(-8.3, -2.4)	(-15.6, -9.6)	(-11.5, -3.0)	

Note: p-value from a restricted maximum likelihood (REML) based repeated-measures analysis of change from baseline, testing whether the LS Means for the two treatments are equal. The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, and the MG-QOL15 total score at baseline. Missing MG-QOL15 total score values were not imputed.

[Source: Sponsor]

Table 3-33 Change from Baseline in MG-QoL15 Total Score at Week 26 and Other Study Visits: (RMM; Ranked on actual changes; Including IST treatment status; FAS)

Variable		Statistic	Placebo (N=63)	Eculisumab (N=62)	Difference in LS Means and 95% CI	p-value
Week	4	n	61	61		0.0429
		LS Means (SEM)	-4.8 (1.32)	-8.3 (1.34)	-3.5	
		95% CI for LS Mean	(-7.4, -2.2)	(-11.0, -5.7)	(-6.9, -0.1)	
Week	8	n	62	57		0.0002
		LS Means (SEM)	-4.1 (1.43)	-11.4 (1.47)	-7.2	
		95% CI for LS Mean	(-7.0, -1.3)	(-14.3, -8.4)	(-11.0, -3.4)	
Week	12	n	61	57		0.0220
		LS Means (SEM)	-7.2 (1.58)	-12.2 (1.62)	-5.0	
		95% CI for LS Mean	(-10.4, -4.1)	(-15.4, -9.0)	(-9.2, -0.7)	
Week	16	n	60	58		0.0096
		LS Means (SEM)	-7.3 (1.61)	-13.0 (1.65)	-5.7	
		95% CI for LS Mean	(-10.5, -4.1)	(-16.3, -9.8)	(-10.0, -1.4)	
Week	20	n	61	57		0.0036
		LS Means (SEM)	-6.8 (1.59)	-13.2 (1.63)	-6.4	
		95% CI for LS Mean	(-9.9, -3.6)	(-16.4, -9.9)	(-10.6, -2.1)	
Week	26	n	60	57		0.0009
		LS Means (SEM)	-6.7 (1.56)	-13.8 (1.60)	-7.1	
		95% CI for LS Mean	(-9.8, -3.6)	(-17.0, -10.7)	(-11.3, -3.0)	

Note: p-value from a restricted maximum likelihood (REML) based repeated-measures analysis of change from baseline, testing whether the LS Means for the two treatments are equal.
The model included the following terms: treatment, visit, the treatment by visit interaction term, the pooled MGFA randomization stratification variable, the MG-QOL15 total score at baseline, and IST treatment status.
Missing values were not imputed.

[Source: Sponsor]

Table 3-34 Change from Baseline in MGC-QoL15 Score at Week 26 (ANCOVA; FAS)

Variable	Statistic	Placebo (N = 63)	Eculizumab (N = 62)	Difference in LS Means and 95% CI	p-value
Change from Baseline (1)	LS Mean (SEM)	-6.0 (1.49)	-11.3 (1.50)	-5.2	0.0152
	95% CI for LS Mean	(-8.99, -3.08)	(-14.24, -8.28)	(-9.43, -1.03)	
Baseline MG-QoL15 Total	n	63	62		
	Mean (SD)	30.7 (12.72)	33.6 (12.21)		
	Median	31.0	33.5		
	Min, Max	6, 60	6, 59		
Week 26 MG-QoL15 Total Score (LOCF)	n	63	62		
	Mean (SD)	25.0 (13.66)	22.2 (16.88)		
	Median	24.0	20.0		
	Min, Max	3, 58	0, 59		
Change from Baseline to Week 26 in MG-QoL15 Total	n	63	62		
	Mean (SD)	-5.7 (9.54)	-11.5 (14.09)		
	Median	-5.0	-9.5		
	Min, Max	-30, 16	-44, 19		

(1) LS Means are from the ANCOVA model.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Max = maximum; MG-QoL15 = Myasthenia Gravis Quality of Life 15-item scale; Min = minimum; SD = standard deviation; SEM = standard error of the mean.

Note: p-value from ANCOVA analysis of change from baseline, testing for the effect of treatment, with the baseline value and the pooled MGFA randomization stratification variable as covariates in the model. For patients who did not require rescue therapy, if the Week 26 MG-QOL15 total score was missing or an item from the Week 26 MG-QOL15 was missing, last observation carried forward (LOCF) was used for missing Week 26 MG-QOL15 total score or missing item of the Week 26 MG-QOL15. For patients requiring For patients requiring rescue therapy, the last observation prior to the first use of rescue therapy was used. If the last observation prior to the first use of rescue therapy was missing an item from the MG-QOL15, last observation carried forward was used for the missing item

[Source: Sponsor]

3.2.1.4.4 Subgroup Analyses

The following tables summarize change from Baseline in MG-ADL, QMG, MGC total score and MG-QoL15 at Week 26 by treatment arm by age, gender, and race based on the FAS. The change in 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.

Table 3-35 Subgroup Analyses Results for MG-ADL

Subgroup: Gender		Placebo	Eculizumab
Female	N	40	38
	Mean (SD)	-1.5 (4.2)	-5.8 (5.25)
Male	N	20	18
	Mean (SD)	-2.1 (3.9)	-3.3 (4.7)
Subgroup: Age		Placebo	Eculizumab
<65 years	N	49	47
	Mean (SD)	-2.1 (3.4)	-4.6 (4.5)
>=65 years	N	11	10
	Mean (SD)	-3.4 (2.5)	-3.3 (3.7)
Subgroup: Race		Placebo	Eculizumab
Asian	N	16	3
	Mean (SD)	-3.1 (3.8)	-1.3 (2.1)
Black	N	2	NA
	Mean (SD)	-0.5 (2.1)	NA
White	N	40	48
	Mean (SD)	-2.0 (3.1)	-4.4 (4.4)
Other/Multiple/Unknown	N	2	5
	Mean (SD)	-3.5 (3.54)	-7.4 (2.7)

Note: Only patients with both baseline and Week 26 values were included in the summary.

The change in QMG 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.

Table 3-36 Subgroup Analyses Results for QMG

Subgroup: Gender		Placebo	Eculizumab
Female	N	40	38
	Mean (SD)	-2.5 (3.4)	-5.4 (4.2)
Male	N	20	19
	Mean (SD)	-2.0 (3.2)	-2.4 (4.0)
Subgroup: Age		Placebo	Eculizumab
<65 years	N	49	47
	Mean (SD)	-1.5 (4.2)	-5.2 (5.5)
>=65 years	N	11	9
	Mean (SD)	-2.4 (3.3)	-4.0 (2.7)
Subgroup: Race		Placebo	Eculizumab
Asian	N	16	3
	Mean (SD)	-0.5 (5.1)	2.0 (5.2)
Black	N	2	NA
	Mean (SD)	-4.5 (3.5)	NA
White	N	40	48
	Mean (SD)	-1.8 (3.6)	-5.5 (4.9)

Other/Multiple/Unknown	N	2	6
	Mean (SD)	-4.5 (2.1)	-4.3 (5.4)

Note: Only patients with both baseline and Week 26 values were included in the summary.

The change in MGC 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.

Table 3-37 Subgroup Analyses Results for MGC

Subgroup: Gender		Placebo	Eculizumab
Female	N	40	38
	Mean (SD)	-4.6 (7.2)	-9.6 (8.7)
Male	N	20	19
	Mean (SD)	-5.5 (6.3)	-6.4 (7.3)
Subgroup: Age		Placebo	Eculizumab
<65 years	N	49	47
	Mean (SD)	-4.4 (6.8)	-8.7 (8.8)
>=65 years	N	11	10
	Mean (SD)	-7.2 (6.8)	-7.7 (5.7)
Subgroup: Race		Placebo	Eculizumab
Asian	N	16	3
	Mean (SD)	-4.2 (8.6)	-0.7 (4.2)
Black	N	2	NA
	Mean (SD)	-3.0 (0.0)	NA
White	N	40	48
	Mean (SD)	-5.2 (6.5)	-9.0 (8.1)
Other/Multiple/Unknown	N	2	6
	Mean (SD)	-6.0 (1.4)	-8.7 (10.1)

Note: Only patients with both baseline and Week 26 values were included in the summary.

The change in MG-QoL15 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.

Table 3-38 Subgroup Analyses Results for MG-QoL15

Subgroup: Gender		Placebo	Eculizumab
Female	N	40	38
	Mean (SD)	-5.4 (9.2)	-16.5 (14.3)
Male	N	20	19
	Mean (SD)	-5.0 (10.1)	-5.7 (10.9)
Subgroup: Age		Placebo	Eculizumab
<65 years	N	49	47
	Mean (SD)	-4.2 (9.7)	-13.7 (14.6)

>=65 years	N	11	10
	Mean (SD)	-9.8 (6.4)	-9.0 (11.7)
Subgroup: Race		Placebo	Eculizumab
Asian	N	16	3
	Mean (SD)	-6.3 (11.5)	-1.3 (11.0)
Black	N	2	NA
	Mean (SD)	-15.5 (14.8)	NA
White	N	40	48
	Mean (SD)	-4.3 (8.4)	-12.7 (13.8)
Other/Multiple/Unknown	N	2	6
	Mean (SD)	-6.5 (0.7)	-20.0 (16.0)

Note: Only patients with both baseline and Week 26 values were included in the summary.

3.3 Evaluation of Safety

Please see the medical officer's review for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS (post baseline)

Since the sample size of the study is small, findings in subgroup populations have limitation in interpretation as shown in Section Subgroup Analyses.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Following the SAP Version 3, three clinically improved but discontinued patients were placed in the clinically deteriorated rescue cohort. These patients in the Eculizumab arm discontinued due to an AE, were not identified by the physician as in need of rescue therapy, did not receive rescue therapy, and did not fulfill the pre-specified clinical deterioration criteria sufficient for rescue therapy. Each of these 3 discontinued patients individually fulfilled the pre-specified criteria for significant clinical improvement. The re-analysis of the data following the SAP Version 2 is deemed clinically justifiable per the discussion during the Type C meeting dated 9/14/2016.

The trial integrity was challenged by changing data for 7 subjects after database lock. Per the email dated 8/7/2017, the field investigator was able to verify the data for the 7 subjects for whom data was changed when the database was unlocked. There was no evidence that any data was changed after the data was originally locked (other than the 7 subjects as indicated by the sponsor). The field investigator did not identify any issues related to data integrity.

5.2 Collective Evidence

In addition to this pivotal study ECU-MG-301, supportive evidence comes from the follow-up study ECU-MG-302 and an early phase 2 study. Please see the medical officer's review of these studies.

5.3 Conclusions and Recommendations

Study ECU-MG-301 shows that Eculizumab has a significant treatment effect on the primary endpoint of interest: change from baseline in Myasthenia Gravis – Activities of Daily Living (MG-ADL) total score at Week 26 ($p = 0.014$ based on worst rank analysis (SAP2)). This analysis which was based on SAP2 is deemed clinically justifiable per the discussion during the Type C meeting dated 9/14/2016.

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/s/

JUNSHAN QIU
09/21/2017

KUN JIN
09/21/2017
I concur with the review.

HSIEN MING J HUNG
09/21/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166Orig1s422

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number:	125166 S422
Submission Date:	12/23/2016
Submission Type:	Efficacy Supplement
Brand Name:	Soliris®
Generic Name:	Eculizumab
Dosage Form and Strength:	Solution. 5 mg/mL. Infusion volume 180 mL for 900 mg doses or 240 mL for 1200 mg doses
Route of Administration:	Intravenous
Proposed Indication:	(b) (4) [redacted]
Applicant:	Alexion Pharmaceuticals, Inc.
OCP Review Team:	Atul Bhattaram, Ph.D. Kevin Krudys, Ph.D. Sreedharan Sabarinath, Ph.D.

1. Executive Summary

Eculizumab is a recombinant monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9 and C5a. Per sponsor, eculizumab inhibits:

- Terminal complement mediated intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH).
- Complement-mediated thrombotic microangiopathy (TMA) in patients with atypical hemolytic uremic syndrome (aHUS).
- Terminal complement-mediated neuromuscular damage in gMG patients.

Eculizumab is indicated for the treatment of patients with

- PNH to reduce hemolysis
- aHUS to inhibit complement-mediated thrombotic microangiopathy.

Sponsor is seeking a third indication, which is

- (b) (4)

The approved dosing regimens for PNH and proposed dosing regimen for (b) (4) gMG are shown in **Table 1**.

Table 1. Eculizumab Dosing Regimens (Approved and Proposed).

Indication	Dosing Regimen
PNH	600 mg weekly for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter.
aHUS	900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter.
gMG	900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter.

Sponsor evaluated dosing regimens approved for PNH and aHUS indications in the development program for (b) (4) gMG. The pilot study C8-001 evaluated the dosing regimen approved for PNH while the pivotal study ECU-MG-301 evaluated the dosing regimen approved for aHUS. Reduction in MG-ADL score was observed in C8-001, consistent with Study ECU-MG-301, suggesting that Study C8-001 can provide supportive evidence of effectiveness (**Figure 3**). No additional clinical pharmacology studies have been submitted in this regulatory cycle.

Population pharmacokinetic analyses have been conducted to add relevant information in the label and edits have been suggested by the review team

2. Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in BLA 125166 S422. Findings that provide support towards approval and specific labeling recommendations are summarized below:

Supportive evidence for the proposed dosing regimen	Study C8-001 showed reductions in MG-ADL score with 600 mg induction and 900 mg maintenance dose. While this dose is lower than that studied in pivotal study (ECU-MG-301, 900 mg induction and 1200 mg maintenance dose), the trends in MG-ADL score reduction, in Study C8-001, provide support towards overall evidence of effectiveness.
Labeling:	Changes in Section 12.3 are provided.

3. Key Review Questions:

3.1 Does Study C8-001 provide supportive evidence of effectiveness?

Yes. Changes in MG-ADL score from Study C8-001 can provide supportive evidence of effectiveness.

Background on Study C8-001: The objectives of this study were to assess the safety and efficacy of eculizumab in patients with generalized Myasthenia Gravis (gMG) who had moderate to severe muscle weakness despite treatment with immunosuppressants. While the primary endpoint of this study was the percentage of patients with a 3-point reduction from baseline in the Quantitative Myasthenia Gravis (QMG) total score for disease severity at the end of the each 16-week treatment period, information on MG-ADL (primary endpoint for study ECU-MG-301) was also collected. Diagnosis of MG was based on a positive serologic test for binding anti-AChR antibodies at screening in addition to other criteria outlined in the protocol.

Briefly, MG-ADL consists of items shown in **Table 2**.

Table 2. MG Activities of Daily Living (MG-ADL) Profile.

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

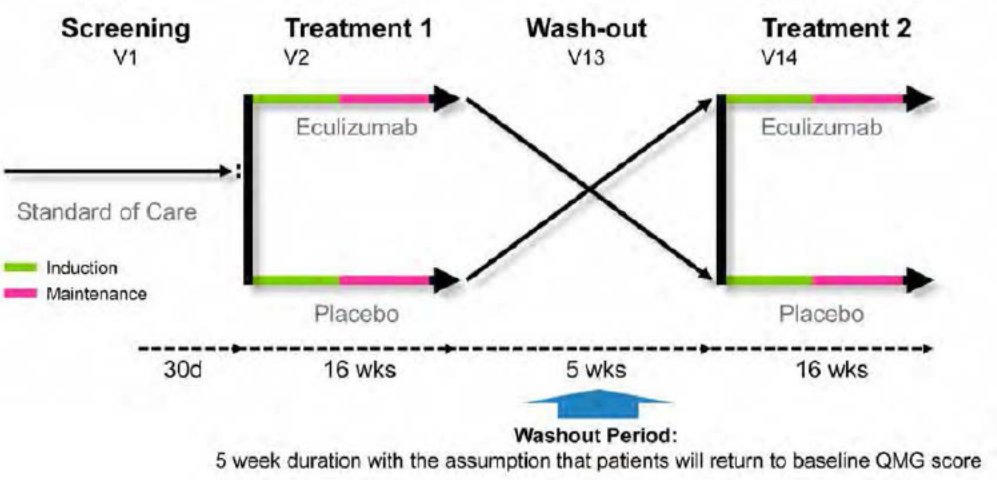
Source : Muppidi et al . MG-ADL: STILL A RELEVANT OUTCOME MEASURE Muscle Nerve 44: 727–731, 2011

Study C8-001 was a randomized, double blind, placebo-controlled trial in which about one half of patients were randomly assigned to each of the following two (A and B) treatment sequences:

(A) Eculizumab treatment, then a 5-week washout period, followed by placebo treatment
(B) Placebo treatment, then a 5-week washout period, followed by eculizumab treatment

The two treatment periods were 16 weeks and the wash-out period was 35 days. (**Figure 1**).
A total of 14 patients were treated and analyzed. Patients received eculizumab according to the following regimens:
Induction Period: Patients received either eculizumab 600 mg or matching placebo via intravenous (IV) infusion once a week (every 7 ± 2 days) for 4 weeks followed by eculizumab 900 mg or matching placebo for the fifth dose 7 ± 2 days later.
Maintenance Period: Patients received either eculizumab 900 mg or matching placebo via IV infusion every 2 weeks (every 14 ± 2 days) for 6 doses.

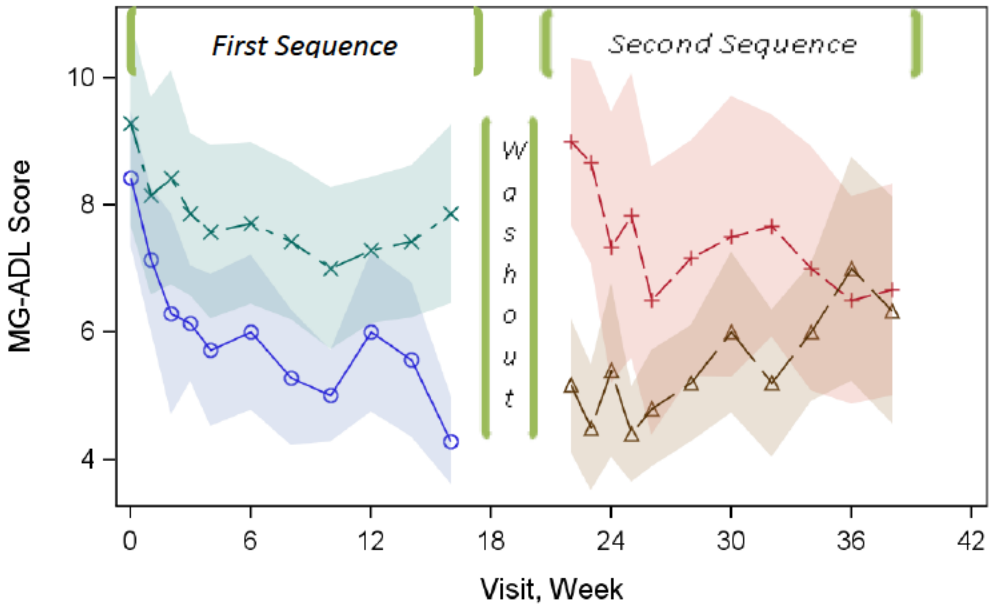
Figure 1. C8-001 Study Design.



Source : Figure 1 on Page 27 in ecu-mg-adult-pk-pd-study-report.pdf

The mean (± 1 standard error) changes in MG-ADL score (findings from Study C8-001 are shown in **Figure 2** .

Figure 2. Changes in MG-ADL Score in Study C8-001. Shown are the data from two sequences in the study (First Sequence : Eculizumab (o) ; Placebo (x)) ; (Second Sequence : Eculizumab (+) ; Placebo (Δ).



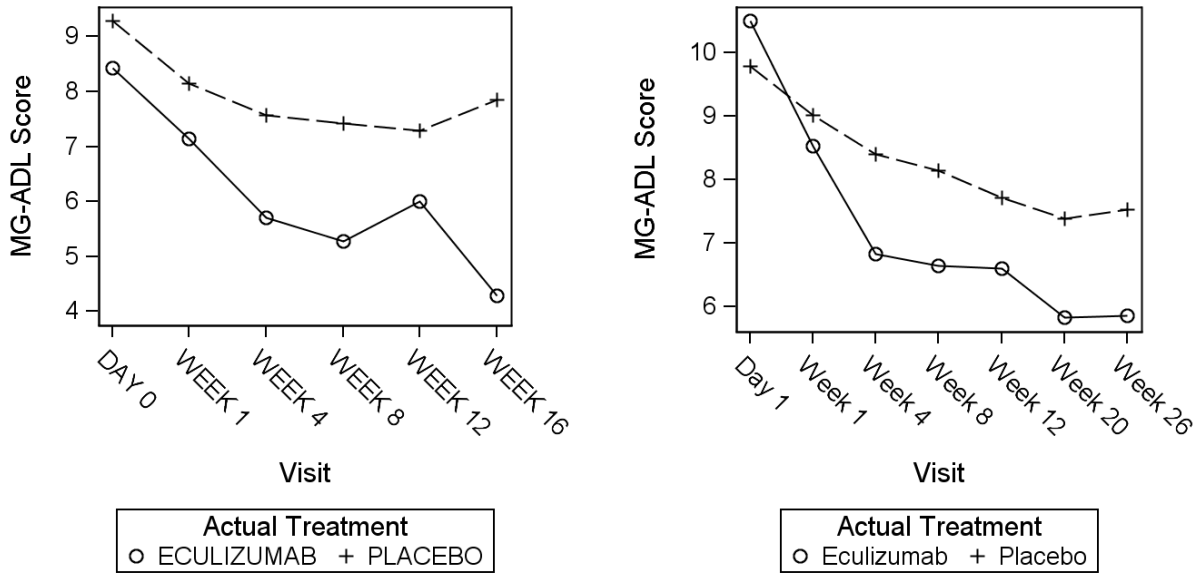
Source: Reviewer analysis

At the end of second sequence, differences between eculizumab and placebo groups could not be established. This was attributed to inadequate washout duration after the first sequence in the study.

The reviewer agrees with the sponsor that washout duration of 5 weeks was not adequate. This can be visualized by the MG-ADL score at the first visit in the group of patients assigned to eculizumab in first sequence (o) followed by placebo in second sequence (Δ). The reported half-life of eculizumab is 272±82 h which is approximately 11 days. Based on the PK half-life alone, washout duration of 5 weeks is not adequate. The sponsor conducted analyses (t-test) of the data obtained in the first sequence (**Figure 2**) and reported a difference (Trt-Plb) of -3.57 units (p = 0.041) in MG-ADL score at the end of 16 weeks in first sequence . However, the analysis of change from baseline in MG-ADL score shows a difference (Trt-Plb) of -2.71 units (p=0.129) at the end of 16 weeks in first sequence. The differences between the two analyses are due to imbalance in mean MG-ADL score at baseline. The reviewer was able to confirm these findings.

Figure 3 compares the changes in MG-ADL score in Study C8-001 (first sequence) and pivotal study ECU-MG-301. The trends in reduction of MG-ADL score can be seen in both studies although placebo-corrected changes are different **(Figure 3**).

Figure 3. Changes in MG-ADL Score by Week in Study C8-001 and ECU-MG-301.

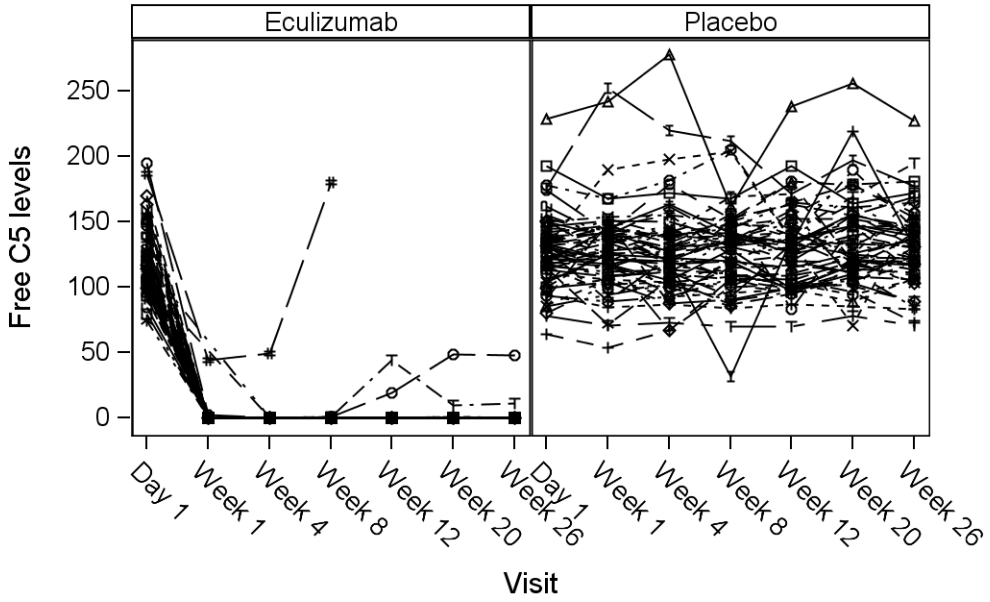


Study C8-001 (first sequence) **Pivotal Study ECU-MG-301**

Source: Reviewer analysis

Considering the mechanism of action, it is expected that lower levels of free C5 (complement component) will be observed in patients treated with eculizumab compared to placebo. **Figure 4** shows the reduction in free C5 levels in placebo and eculizumab treated groups from Study ECU-MG-301. Except for 3 patients in eculizumab treated group, lowering of free C5 levels were seen in all other patients.

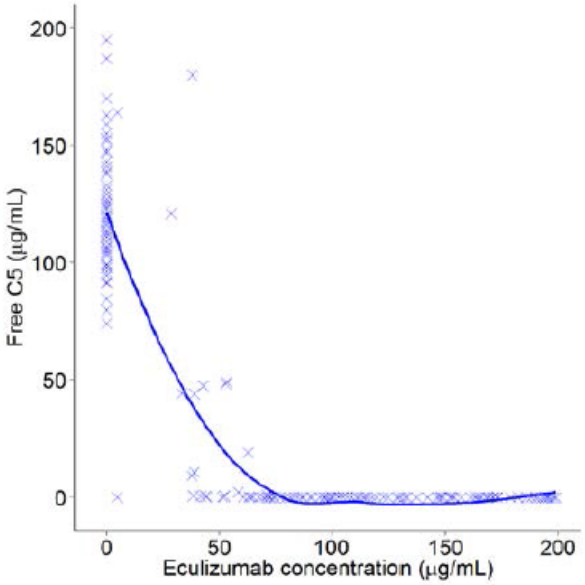
Figure 4. Free C5 Levels in Eculizumab and Placebo Groups at Various Visits in Study ECU-MG-301



Source: Reviewer analysis

It should be noted that patients in study ECU-MG-301 received a higher eculizumab induction/maintenance dose (900/1200 mg) when compared to study C8-001 (600/900 mg). The dosing regimens studied in Study C8-001 and ECU-MG-301 (**Figure 6**) resulted in patients achieving concentrations (for lowering C5 levels) of at least 100 μg/mL (**Figure 5**), which support the efficacy findings at both dose levels as shown in **Figure 3**.

Figure 5. Scatter Plot of Free C5 Concentration Vs Eculizumab Concentration in Study ECU-MG-301



Source : Figure 14 on Page 73 in ecu-mg-adult-pk-pd-study-report.pdf

Overall, one could conclude that eculizumab has shown trends in the right direction in Study C8-001 for MG-ADL score and it adds support to the findings from another independent study ECU-MG-301.

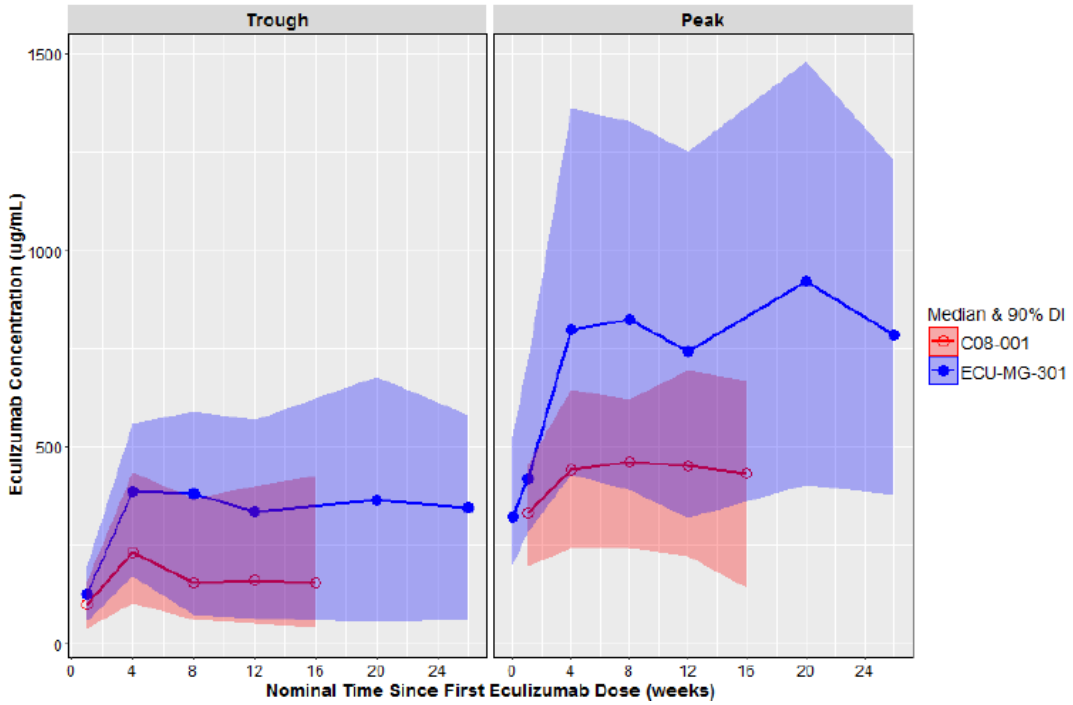
3.2 Are the proposed labeling statements based on population pharmacokinetic analyses in section 12.3 of the label acceptable?

No. The proposed labeling statements regarding parameter estimates for clearance and volume of distribution are not acceptable due to:

- Unexpected differences in eculizumab concentrations from Studies C8-001 and ECU-MG-301 which necessitated the inclusion of analytical method as a covariate in the population pharmacokinetic analyses. No information on cross-validation of analytical methods used in Study C8-001 and ECU-MG-301 is available. Alternate labeling language is being suggested by the review team.

Figure 6 shows the dose normalized eculizumab concentrations in Study C8-001 and ECU-MG-301.

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



Source : Figure 4 on Page 49 in ecu-mg-adult-pk-pd-study-report.pdf

Eculizumab concentrations in Study ECU-MG-301 were 2-fold higher than the concentrations observed in Study C8-001. Sponsor investigated various causes for these differences by focusing on:

- Bioanalytical investigation
- Product quality investigation and review of Chemistry, Manufacturing and Controls (CMC) information
- Clinical pharmacology assessment

Sponsor states that the current bioanalytical assay used to measure eculizumab in Study ECU-MG-301 was compliant with all applicable regulatory guidelines. This aspect was reviewed by DARS (See attached review) and the assay was found to be fit-for-purpose. However, the sponsor could not conduct cross-validation of the analytical methods used in Study C8-001 and

ECU-MG-301. Per sponsor, no drug product-related characteristics could be identified that could explain differences in PK between the two studies. These differences were also not attributed to any intrinsic/extrinsic factors that could influence eculizumab concentrations.

Sponsor's population pharmacokinetic analyses, that included an assay factor to describe the differences in eculizumab concentrations across studies, were reviewed. Since no specific reason could be identified for the differences in eculizumab concentrations between studies and the approval decision will largely be based on findings from Study ECU-MG-301, the review team decided to include information on observed eculizumab concentrations from Study ECU-MG-301 in the product label. Similar information from PNH indication is in the current label.

The proposed labeling language, based on reviewer's summary analysis of eculizumab concentrations from Study ECU-MG-301 is:

(b) (4)

3.3 Are the proposed labeling statements regarding pharmacodynamic effects in Section 12.2 of the label acceptable?

Yes. The proposed labeling language is acceptable.

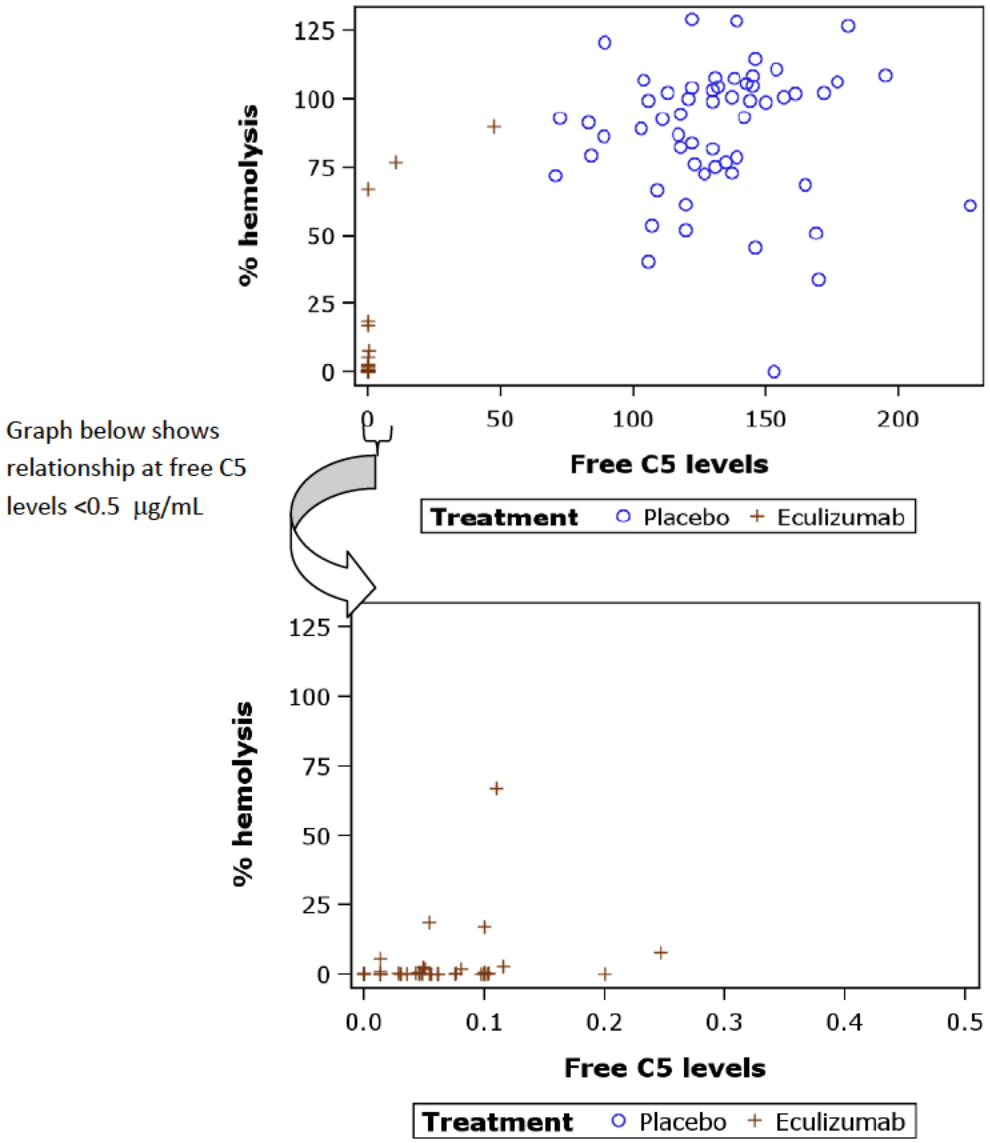
Sponsor proposed language is shown below:*In patients with PNH, aHUS, and gMG, free C5 concentrations of < 0.5 mcg/mL was correlated with complete blockade of terminal complement activity.*

This statement is based on correlation between free C5 concentrations and the complete inhibition of terminal complement, cRBC hemolysis (<20%).

Chicken RBC hemolytic activity in Study C08-001 and ECU-MG-301 samples was expressed relative to different single pools of normal human serum (NHS), respectively. The cRBC hemolytic assay is a semi-quantitative assay and <20% hemolysis represents complete terminal complement inhibition. Conclusions based on inhibition of hemolysis by eculizumab are included in current approved label for PNH and aHUS indications.

Figure 7 shows the relationship between cRBC hemolysis and free C5 concentrations in Study ECU-MG-301 (pre-dose, Week 26). The data suggests almost complete blockade of terminal complement activity at free C5 concentrations of < 0.5 mcg/mL. These findings support the proposed labeling statements.

Figure 7. Relationship between % hemolysis and free C5 levels (mcg/mL) in Study ECU-MG-301



Source: Reviewer analysis

Date: 10 July 2017

From: James Weaver PhD, Division of Applied Regulatory Science/Office of Clinical Pharmacology (DARS/OCP)

Through: David Strauss MD, PhD, Director; DARS/OCP

To: Atul Bhattaram & Kevin Krudys, DP/OCP and Sreedharan Sabarinath, DCP1/OCP

Subject: Evaluation of ELISA to measure Eculizumab in patient plasma samples.

Executive Summary

The ELISA method for quantitation of Eculizumab in human plasma was validated in accordance with the standards defined in the FDA Bioanalytical Methods Validation guidance. The performance of the assay during analysis of the clinical samples met the Guidance-specified QC standards. Incurred sample reanalysis was completed and also met the standards. This assay is fit for purpose.

Background

Eculizumab is a monoclonal antibody approved in 2007 for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). This disease is caused by a defect in anchoring of CD55, a cell surface protein that inactivates the C3 convertase that cleaves C5 to its biologically active C5a and C5b forms. This defect results in poorly controlled episodes of complement activation leading to major hemolysis in circulation.

The therapeutic protein is a hybrid with sequences from human IgG2, IgG4 and from the murine anti-human C5 antibody binding site. The monoclonal antibody acts by binding intact human C5 and preventing the cleavage to C5a and C5b.

The sponsor is seeking approval for additional indications and has submitted ELISA data on circulating levels of the drug in patients.

Questions in the Consult request from OCP:

1. *Is the ELISA assay method used here acceptable for bioanalysis - Is it validated as per FDA guidelines?*

2. *Is the sample analysis using this method acceptable - i.e., QC samples passed acceptance criteria and incurred sample re-analyses were acceptable?*

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

Evaluation

The sponsor, Alexion Pharmaceuticals, contracted with [redacted] to develop and validate the method and to perform the measurements of the concentration of Eculizumab in the clinical trial plasma samples. The assay validation study was reported as Study [redacted] and the clinical samples measurements study was # [redacted]. Both studies were submitted by the sponsor under sBLA 125166 and were performed in accordance with GLP regulations.

Assay description: The assay is of a conventional ELISA assay design, the [redacted] All reagents except for the reference material were commercially available. The reference material was pure Eculiziumab as supplied by the sponsor and used with the specifications as supplied by the sponsor.

Assay validation: The contractor performed the following studies as method validation and as described in report [redacted]

- "Accuracy and Precision
  - Intra-Assay Variation
  - Inter-Assay Variation
- Dilutional Linearity
- Selectivity
  - Normal Matrix
  - Hemolyzed Matrix
- Stability
  - Short Term Storage Stability (STS)
  - Freeze/Thaw Cycle Stability (FTS)
  - Long Term Storage Stability (LTS)"

The performance criteria as set by the contractor are in agreement with the criteria recommended in the FDA Bioanalytical Methods Validation guidance.

The calibration curve included seven quantified concentrations including the lower and upper limits of quantitation of [redacted] µg/ml respectively. Two anchor concentrations of [redacted] µg/ml were included as recommended to improve the curve fitting. All performance criteria for this assay were met.

1. *Is the ELISA assay method used here acceptable for bioanalysis - Is it validated as per FDA guidelines?*
   Yes. The method validation studies performed by the contractor were those recommended in the FDA guidance and the performance criteria are those suggested in the FDA Guidance. The results of the validation studies reported by the contractor show that the actual performance of the assay during validation studies was acceptable based on the performance criteria set by the FDA Bioanalytical Methods Validation guidance.

   Assay Performance: The actual performance of the assay in measuring [redacted] clinical trial samples

is reported in summary form in document (b) (4). This document includes the results of the pharmacokinetic analysis as well as a number of other studies that will not be evaluated here. Data reported for the PK assay in Appendix B include standard curve (Table 2), QC sample results (Table 3) and incurred sample reanalysis (Table 5).

2. *Is the sample analysis using this method acceptable - i.e., QC samples passed acceptance criteria and incurred sample re-analyses were acceptable?*
   Assay performance as judged by standard curve data was acceptable and was comparable to the data reported in the methods validation study. The contractor reported a total of (b) (4) analytical assay runs and 11 runs were rejected because QC acceptance criteria were not met. The samples were reanalyzed and QC criteria were met. The summary statistics for the QC data for accepted runs show that the performance was within accepted limits. Incurred sample reanalysis was performed on a total of (b) (4) samples. The number reanalyzed is above the (b) (4) threshold of (b) (4) samples and the pass rate was (b) (4), above the limit of 66.7% specified in the FDA guidance.

Summary and Conclusions

In conclusion, the ELISA method for quantitation of Eculizumab was validated in accordance with the standards defined in the FDA Bioanalytical Methods Validation guidance. The performance of the assay during analysis of the clinical samples met the Guidance-specified QC standards. Incurred sample reanalysis was completed and also met the standards. This assay is fit for purpose.

References and Supporting Documents

FDA - Guidance for Industry, Bioanalytical Method Validation, DRAFT GUIDANCE, September 2013. https://www.fda.gov/downloads/Drugs/Guidances/ucm368107.pdf (accessed 6 July 2017).

From sBLA 125166:

(b)(4)

(b)(4)

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/s/

VENKATESH A BHATTARAM
09/26/2017

KEVIN M KRUDYS
09/26/2017

SREEDHARAN N SABARINATH
09/26/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166Orig1s422

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****
Memorandum

Date: October 18, 2017

To: Michelle Mathers, Regulatory Project Manager
Division of Neurology Products (DNP)

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Aline Moukhtara, Regulatory Reviewer Officer, OPDP

Subject: **BLA 125166/s422**
OPDP labeling comments for SOLIRIS® (eculizumab) injection, for intravenous use (Soliris)

In response to DNP's consult request dated February 14, 2017, OPDP has reviewed the draft product labeling (PI), medication guide, and carton/container labeling for Soliris for the treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive.

PI:

OPDP's comments on the draft PI for Soliris are based on the version of the PI downloaded from SharePoint on October 17, 2017, and are provided below.

Medication Guide:

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on September 25, 2017.

Carton/Container Labeling:

OPDP has reviewed the attached carton/container labeling for Soliris provided by DNP (Michelle Mathers) via email on October 17, 2017, and has no comments at this time.

If you have any questions, please feel free to contact me by phone at 301-796-6796 or by email at Christine.Bradshaw@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials. Thank you!

45 Page(s) of Draft Labeling Witheld in Full as b4(CCI/TS) Immediately Following this Page

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/s/

CHRISTINE J BRADSHAW
10/18/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	September 25, 2017
To:	Billy Dunn, MD Division Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Acting Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Mathilda Fienkeng, PharmD, RAC Team Leader **Office of Prescription Drug Promotion (OPDP)**
From:	Twanda Scales, RN, BSN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Aline M. Moukhtara, RN, MPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	SOLIRIS (eculizumab)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 125166
Supplement Number:	S-422
Applicant:	Alexion Pharmaceuticals, Inc.

1 INTRODUCTION

On December 23, 2016, Alexion Pharmaceuticals, Inc. submitted for the Agency's review a Supplemental Biologic License Application (sBLA) for SOLIRIS (eculizumab) injection, for intravenous use in the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (anti-AChR) antibody positive. SOLIRIS (eculizumab) injection, for intravenous use was originally approved March 16, 2007 and is currently indicated for the treatment of patients with:

- paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.
- atypical uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on February 14, 2017, for DMPP and OPDP to review the Applicant's proposed Medication Guide for SOLIRIS (eculizumab) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft SOLIRIS (eculizumab) injection, for intravenous use MG received on December 23, 2016 and received by DMPP on September 18, 2017.
- Draft SOLIRIS (eculizumab) injection, for intravenous use Prescribing Information (PI) received on December 23, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on September 18, 2017.
- Draft SOLIRIS (eculizumab) injection, for intravenous use MG received on December 23, 2016, and received by OPDP on September 20, 2017.
- Draft SOLIRIS (eculizumab) injection, for intravenous use Prescribing Information (PI) received on December 23, 2016, revised by the Review Division throughout the review cycle, and received by OPDP on September 20, 2017.

3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
09/25/2017

ALINE M MOUKHTARA
09/25/2017

LASHAWN M GRIFFITHS
09/25/2017

MEMORANDUM

Date: June 6, 2017

To: File for BLA 125166

From: Brenda J Gehrke, PhD
Pharmacology-Toxicology Reviewer
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)

Through: Christopher Sheth, PhD
Pharmacology-Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)

Subject: Labeling changes to Soliris label: Conversion to PLLR format
BLA: 125166
Drug: Soliris (eculizumab)
Applicant: Alexion Pharmaceuticals, Inc.

The current submission, Supporting Document 1120 (eCTD Sequence 0572) for BLA 125166, is an efficacy supplement (Supplement 422) for Soliris. Soliris (eculizumab) is a complement inhibitor currently approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis and patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. The current efficacy supplement is for a new indication for the treatment of [redacted] (b) (4) . The efficacy supplement required the Soliris label to be converted into the Pregnancy and Lactation Labeling Rule (PLLR format); therefore, the Applicant proposed PLLR labeling changes to the pregnancy related sections of the prescribing information. These changes were reviewed and additional changes and edits were made to be consistent with the PLLR labeling format.

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/s/

BRENDA J GEHRKE
06/06/2017

CHRISTOPHER M SHETH
06/06/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 11, 2017
Requesting Office or Division:	Division of Neurology Products
Application Type and Number:	BLA 125166/S-422
Product Name and Strength:	Soliris (eculizumab) injection, 300 mg/30 mL (10 mg/mL)
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Alexion
Submission Date:	December 23, 2016; April 6, 2017
OSE RCM #:	2017-341
DMEPA Primary Reviewer:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

Alexion submitted an efficacy supplement on December 23, 2016 for Soliris (BLA 125166/S-422) which proposes the addition of a new indication for treatment of (b) (4) Thus, the Division of Neurology Products (DNP) requested we evaluate the labels and labeling for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C—N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E—N/A
Other-Proposed changes to the PI and MG	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the revisions proposed to the Prescribing Information (PI) and Medication Guide (MG) for Soliris (BLA 125166) for risk of medication error and did not identify any areas of concern. We note that the efficacy supplement proposes revisions to the PI and MG to support the addition of the indication of the treatment of (b) (4) . We also note that the proposed dosing for the new indication is identical to the currently approved adult dosing for the atypical hemolytic uremic syndrome (aHUS) indication.

As part of our review, we considered whether the proposed revisions to the PI and MG will impact the carton labeling and container labeling. Our evaluation of the revisions did not identify any necessary changes to the carton labeling or container labels.

4 CONCLUSION & RECOMMENDATIONS

The proposed revisions to the Soliris PI and MG are acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Soliris that Alexion submitted on December 23, 2016.

Table 2. Relevant Product Information for Soliris	
Initial Approval Date	N/A
Active Ingredient	eculizumab
Indication	- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis - The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy - (b) (4)
Route of Administration	Intravenous infusion
Dosage Form	Injection solution
Strength	300 mg/30 mL (10 mg/mL)
Dose and Frequency	- *PNH*: o 600 mg weekly for the first 4 weeks, followed by o 900 mg for the fifth dose 1 week later, then o 900 mg every 2 weeks thereafter. - *aHUS and gMG*: o 900 mg weekly for the first 4 weeks, followed by o 1200 mg for the fifth dose 1 week later, then o 1200 mg every 2 weeks thereafter.
How Supplied	Single-dose vial
Storage	Store Soliris vials in the original carton until time of use under refrigerated conditions at 2-8º C (36-46º F) and protected from light. Soliris vials may be held in the original carton at controlled room temperature (not more than 25° C/77° F) for only a single period up to 3 days.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 16, 2017, we searched the L:drive and AIMS using the term, Soliris, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified did not identify any previous review relevant to the current review.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On February 16, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Community Joint Commission Nursing PA Patient Safety
Search Strategy and Terms	Match Exact Word or Phrase: Soliris

D.2 Results

Our search did not identify any newsletter articles.

APPENDIX F. Proposed changes to the PI and MG (excerpted from submission)

The supplement proposes the following revisions:

- Section 2.3 Recommended Dosage Regimen— (b) (4) gMG was added to include dosing information for the new indication.
- Section 2.4 was revised to include editorial edits to the information regarding dose adjustment for plasmapheresis, plasma exchange, or fresh frozen plasma infusion.
- (b) (4) 6.1 Clinical Trial Experience were updated to include information from (b) (4) gMG clinical studies.
- Sections 8.1 Pregnancy and 8.2 Lactation were revised to be in accordance with the Pregnancy and Lactation Labeling Rule.
- Section 8.4 Pediatric Use was updated to include the new indication.
- Section 12 Clinical Pharmacology was updated to include information regarding the mechanism of action for gMG.
- Section 14.3 (b) (4) Generalized Myasthenia Gravis (gMG) was added to include information from refractory gMG clinical studies.
- Medication Guide was updated to reflect the new indication

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Soliris labeling submitted by Alexion on April 6, 2017.

- Prescribing Information (not pictured)
- Medication Guide (not pictured)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

EBONY A WHALEY
04/11/2017

LOLITA G WHITE
04/11/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166Orig1s422

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type	BLA
Application Number	125166/S-422
OSE RCM #	2017-340
Reviewer(s)	Bob Pratt, Pharm.D.
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	October 23, 2017
Subject	Evaluation of REMS Modification – Supplemental application for a new indication
Established Name	Eculizumab
Trade Name	Soliris®
Applicant:	Alexion Pharmaceuticals, Inc.
Formulation	300 mg/10 mL single-use vials (10 mg/mL)
Dosing Regimen	900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter
Indication	Treatment of adult patients with generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor antibody positive

1 Introduction

This is a review of Alexion Pharmaceuticals' (Alexion) proposed Risk Evaluation and Mitigation Strategy (REMS) modification for eculizumab (Soliris®), BLA 125166/S-422, submitted on December 23, 2016 and amended on September 20, 22, and October 20, 23, 2017. The Applicant submitted the REMS modification as part of a supplemental application for a new proposed indication for the (b) (4)

The amended REMS modification proposes editorial changes to the REMS document as well as changes to the REMS appended materials that align with labeling changes related to the myasthenia gravis indication. Alexion agrees to include knowledge assessments of prescribers and patients regarding the safe use of eculizumab for the treatment of myasthenia gravis in the next REMS assessment, and to reinstate such assessments for the paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) indications previously approved.

2 Background

2.1 Product Information

Eculizumab is a humanized monoclonal antibody that binds to complement protein C5 and blocks its cleavage, thereby preventing the production of the terminal complement components C5a and the membrane attack complex C5b-9. Terminal complement-mediated cell damage and inflammation at the neuromuscular junction is believed to play a role in autoantibody-mediated myasthenia gravis at the acetylcholine receptor and other receptor-associated proteins. The recommended eculizumab dose is 900 mg weekly by intravenous infusion for the first 4 weeks, followed by 1200 mg for the fifth dose one week later, then 1200 mg every 2 weeks thereafter.

Eculizumab was originally approved on March 16, 2007 for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH). The approval included a postmarketing commitment for Alexion to submit a comprehensive risk minimization action plan (RiskMAP) to address the risks of meningococcal infection and other serious infections, and the potential risk of discontinuation hemolysis. Following submission of the RiskMAP and subsequent discussions, the Agency determined the RiskMAP should be replaced with a REMS, which was approved on June 4, 2010.[a] The REMS has been modified six times for various reasons since approval.

2.2 Regulatory History

The following is a summary of the regulatory history for BLA 125166/S-422 relevant to this review:

- December 23, 2016: Alexion submitted supplemental BLA 125166/S-422 for the use of eculizumab in the (b) (4)

[a] Although never approved by the Agency, the Applicant voluntarily implemented the proposed RiskMAP after product launch.

(b) (4)[1] The submission included a proposed REMS modification to align the REMS with labeling changes related to the new indication. Alexion also submitted the June 1, 2017 REMS Assessment Report early as part of the submission, as recommended by the Division of Hematology Products (the division responsible for the currently approved indications). The assessment report is being reviewed by DRISK under separate cover.

- January 13, 2017: The Agency approved BLA 125166/S-417, which updated the labeling to modify the recommendations for meningococcal vaccination in patients receiving eculizumab. The approval included modification of the REMS materials to align with the changes to the prescribing information.
- April 3, 2017: The Agency sent an Information Request to Alexion requesting submission of a revised REMS supporting document that aligns with the proposed revisions made to the REMS and REMS materials in S-422, as these changes were not included in the initial submission. The Applicant was also asked to address additional questions that the Agency considers standard when submitting a REMS assessment for a supplemental application for a new indication for use, which is a statutory requirement.
- April 18, 2017: Alexion submitted REMS correspondence to provide a revised REMS supporting document and a response to the additional questions in the REMS assessment for a supplemental application for a new indication in BLA 125166/S-422.[2]
- September 11, 2017: The Agency sent comments by email to Alexion requesting editorial changes to the REMS document and changes to the REMS assessment plan. Alexion was also asked to provide additional details that describe the process of identifying and correcting non-compliance with the REMS requirements.
- September 20, 2017: Alexion submitted REMS correspondence to BLA 125166/S-422 that provided a revised REMS document. The cover letter for the submission described the process of identifying and correcting non-compliance as well as changes that Alexion agreed to make to the REMS assessment plan.[3]
- September 22, 2017: Alexion submitted REMS correspondence to BLA 125166/S-422 to provide a revised REMS supporting document.[4]
- October 4, 2017: The Agency sent comments by email to Alexion requesting additional details regarding the (b) (4) in the REMS compliance plan and to include the compliance plan in the REMS supporting document upon resubmission. Alexion was also reminded to submit amended REMS materials such that the materials reflect and align with the final FDA-approved product labeling.
- October 10, 2017: Alexion submitted REMS correspondence to BLA 125166/S-422 to provide a response to the Agency's Information Request of October 4, 2017.[5]
- October 19, 2017: The Agency sent instructions for final submission of the REMS document, appended REMS materials, and REMS supporting document to Alexion by email.
- October 20, 2017: Alexion submitted an amendment to BLA 125166/S-422 that included a revised REMS document, revised appended materials, and a revised REMS supporting document.[6]
- October 21, 2017: The Agency sent comments by email to Alexion requesting changes to certain REMS materials such that they align with the labeling.

- October 23, 2017: Alexion submitted an amendment to BLA 125166/S-422 that included revised appended materials and a complete REMS.[7]

3 Results of Review of Proposed REMS Modification

The Clinical review concluded that the benefit of eculizumab for the treatment of myasthenia gravis outweighs the risks, with modification of the REMS with the addition of the new indication.[8] Information supporting the benefit of treatment was provided in the Biometrics review, which concluded the pivotal clinical study demonstrates a statistically significant treatment effect of eculizumab on the primary endpoint of interest, the change from baseline in Myasthenia Gravis–Activities of Daily Living total score at Week 26 ($p = 0.0140$).[9]

Alexion incorporated and responded appropriately to the Agency's comments in the October 19, 21, 2017, email communications. DRISK agrees with the changes proposed in the REMS modification, which are outlined below.

3.1 REMS Document

Alexion accepted and incorporated the editorial changes to the REMS document as requested.

3.2 REMS Materials

3.2.1 Medication Guide

The following sections of the Medication Guide were updated to align with the revised prescribing information:

- What is Soliris? Soliris is used to treat adults with a disease called generalized Myasthenia Gravis (gMG) who are anti-Acetylcholine Receptor (AchR) antibody positive.
- What are the possible side effects of Soliris? The most common side effects in people with gMG treated with Soliris include:

The Medication Guide was previously reviewed by the Division of Medical Policy Programs–Patient Labeling Team under separate cover.[10] The Patient Labeling Team recommended additional formatting and language changes to the Medication Guide that the Applicant incorporated.

3.2.2 Prescriber Introductory Letter and Enrollment Form

Under the Indications and Usage, Alexion updated the myasthenia gravis indication statement and common adverse reactions in the MG trials to align with the prescribing information.

3.2.3 Patient Safety Brochure

The same changes as in the Medication Guide described above were incorporated into the Patient Safety Brochure (which includes a copy of the Medication Guide).

3.2.4 Prescriber Safety Brochure

The same changes as in the Medication Guide described above were incorporated into the Prescriber Safety Brochure (which includes a copy of the Medication Guide).

The list of the most frequently reported adverse reactions in the clinical trials was updated to align with the prescribing information.

3.2.5 DOSING AND ADMINISTRATION GUIDE

The Dosing and Administration Guide was updated to align with the revised myasthenia gravis indication statement as well as the common adverse reactions in the MG trials described in the prescribing information. (b) (4) .

3.3 REMS SUPPORTING DOCUMENT AND ASSESSMENT PLAN

Alexion clarified the correct email address to use for prescribers to send the completed prescriber enrollment form to, as requested.

With regard to the REMS compliance plan, Alexion uses a hierarchy of activities to gain compliance if a healthcare provider is found to be non-compliant with the REMS enrollment requirement, elevating the matter to higher levels in the organization. The Alexion (b) (4) is ultimately responsible for identifying next steps and additional tasks necessary to assure REMS enrollment. (b) (4) has not deemed it appropriate to stop drug shipments for non-compliance to date.

Alexion agrees to reinstate the discontinued prescriber and patient surveys, previously requested for PNH and aHUS, to apply to all approved indications including myasthenia gravis. The Applicant will submit the survey methodology protocol at least 90 days prior to administration of the survey. The timetable for submission of assessments is to remain every two years as stated in the currently approved REMS.

Reviewer comment: Changes to the assessment plan will be communicated to Alexion in the REMS 7-Year Assessment Complete letter that is currently pending issuance after the approval of this supplement. For the purpose of the efficacy supplement/REMS modification approval letter, the assessment plan will remain the same as the plan that is currently approved.

4 Conclusion and Recommendations

DRISK finds the proposed REMS modification for eculizumab and its appended materials (attached), and the supporting document, as submitted on October 23, 2017, are acceptable.

DRISK recommends approval of the REMS appended to this review.

5 Appendix

5.1 REFERENCES

[1] Alexion. REMS Modification for eculizumab, BLA 125166 S-422, December 23, 2016.

[2] Alexion. REMS Correspondence, Response to Information Request, BLA 125166 S-422, April 18, 2017.

[3] Alexion, REMS Correspondence, Response to Information Request, BLA 125166 S-422, September 20, 2017.

[4] Alexion, REMS Correspondence, Response to Information Request, BLA 125166 S-422, September 22, 2017.

[5] Alexion, REMS Correspondence, Response to Information Request, BLA 125166 S-422, October 10, 2017.

[6] Alexion, REMS Amendment, BLA 125166 S-422, October 20, 2017.

[7] Alexion, REMS Amendment, BLA 125166 S-422, October 23, 2017.

[8] Breder C. Division of Neurology Products. BLA 125166 S-422, email communication, October 19, 2017.

[9] Qiu, J. Office of Biostatistics. Statistical Review and Evaluation, BLA 125166 S-422, September 21, 2017.

[10] Scales T. Division of Medical Policy Programs. Patient Labeling Review, BLA 125166 S-422, September 25, 2017

65 Page(s) of Draft Labeling (Draft REMS) Witheld in Full as b4(CCI/TS) Immediately Following this Page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT G PRATT
10/23/2017

JAMIE C WILKINS PARKER
10/23/2017

Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type	BLA
Application Number	125166/S-422
OSE RCM #	2017-340
Reviewer(s)	Bob Pratt, Pharm.D.
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	August 31, 2017
Subject	Evaluation of REMS Modification – Supplemental application for a new indication
Established Name	Eculizumab
Trade Name	Soliris®
Applicant:	Alexion Pharmaceuticals, Inc.
Formulation	300 mg/10 mL single-use vials (10 mg/mL)
Dosing Regimen	900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter
Indication	(b) (4)

Table of Contents

Executive Summary

This is a review of Alexion Pharmaceuticals' proposed Risk Evaluation and Mitigation Strategy (REMS) modification for eculizumab (Soliris®), BLA 125166/S-422, submitted on December 23, 2016. The REMS for eculizumab was originally approved on June 4, 2010 to mitigate the risk of meningococcal infection and hemolysis post-discontinuation. The REMS has been modified six times since approval. The most recently approved REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments. The Applicant submitted the REMS modification as part of a supplemental application for a new indication for the (b) (4) .

The Applicant proposes modifications to the REMS appended materials to align with labeling changes related to the new myasthenia gravis indication; the modifications will be acceptable provided that the REMS materials accurately reflect the final version of the labeling, which remains under review at this time. If the modifications currently proposed do not reflect the final version of the labeling (should the supplemental application be approved) the Applicant will need to submit amended REMS materials. The Applicant did not propose any changes to the REMS assessment plan. In considering the addition of a new group of prescribers and patients, DRISK requests an assessment of prescriber and patient understanding regarding the safe use of Soliris for the treatment of myasthenia gravis. Additionally, DRISK finds the prescriber and patient surveys should be reinstated for the PNH and aHUS indications; this in part is due to recent changes to the Advisory Committee on Immunization Practices' meningococcal immunization recommendations, as well as other concerns related to the most recent REMS assessment report that was submitted as part of the efficacy supplement. We also request additional details that describe the process of identifying and correcting non-compliance in the prescribing population, which is expected to increase in number.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed modification to the risk evaluation and mitigation strategy (REMS) for eculizumab (Soliris®), BLA 125166/S-422, submitted by Alexion Pharmaceuticals (Alexion) on December 23, 2016. The Applicant submitted the REMS modification as part of a supplemental application for a new indication for the (b) (4) .

The submission proposes modifications to the REMS appended materials to align with labeling changes related to the new indication. The supplemental application is under review in the Division of Neurology Products (DNP).

2 Background

2.1 Product Information

Eculizumab is a humanized monoclonal antibody that binds to complement protein C5 and blocks its cleavage, thereby preventing the production of the terminal complement components C5a and the

membrane attack complex C5b-9. Terminal complement-mediated cell damage and inflammation at the neuromuscular junction is believed to play a role in autoantibody-mediated myasthenia gravis at the acetylcholine receptor and other receptor-associated proteins. The recommended eculizumab dose is 900 mg weekly by intravenous infusion for the first 4 weeks, followed by 1200 mg for the fifth dose one week later, then 1200 mg every 2 weeks thereafter.

Eculizumab was originally approved on March 16, 2007 for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH). The approval included a postmarketing commitment for Alexion to submit a comprehensive risk minimization action plan (RiskMAP) to address the risks of meningococcal infection and other serious infections, and the potential risk of discontinuation hemolysis. Following submission of the RiskMAP and subsequent discussions, the Agency determined that the RiskMAP should be replaced with a REMS, which was approved on June 4, 2010.[a]

The REMS has been modified six times for various reasons since approval. Approval of a new indication for the treatment of atypical hemolytic uremic syndrome (aHUS) on September 23, 2011 accounted for the first REMS modification.

The goals of the current REMS are:

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To educate Healthcare Professionals and Patients (or Caregivers, or Legal Guardians) regarding:
    - the increased risk of meningococcal infections with Soliris® (eculizumab)
    - the early signs of invasive meningococcal infections, and
    - the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections

The REMS elements consist of a Medication Guide and elements to assure safe use (ETASU) that include certification of prescribers to counsel and provide educational materials to patients, as well as to report cases of meningococcal infection to the Applicant. The REMS also contains a timetable for the submission of assessments, which requires submission every two years as of June 2015.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 125166/S-422 relevant to this review:

- June 4, 2010: Eculizumab REMS approved.
- June 12, 2014: Orphan product designation granted for the treatment of myasthenia gravis.
- December 23, 2016: Alexion submitted supplemental BLA 125166/S-422 for the use of eculizumab in the treatment of patients with generalized myasthenia gravis who are anti-acetylcholine receptor antibody positive. The submission included a proposed REMS modification to align the REMS with labeling changes related to the new indication. Alexion also submitted the June 1, 2017 REMS Assessment Report early as part of the submission, as recommended by the Division of Hematology

[a] Although never approved by the Agency, the Applicant voluntarily implemented the proposed RiskMAP after product launch.

Products (the division responsible for the approved indications). The assessment report is being reviewed by DRISK under separate cover.

- January 13, 2017: The Agency approved BLA 125166/S-417, which updated the labeling to modify the recommendations for meningococcal vaccination in patients receiving eculizumab. The approval included modification of the REMS materials to align with the changes to the prescribing information.
- April 3, 2017: The Agency sent an Information Request to Alexion requesting submission of a revised REMS supporting document that aligns with the proposed revisions made to the REMS and REMS materials in S-422. The Applicant was also asked to address additional questions that the Agency considers standard when submitting a REMS assessment for a supplemental application for a new indication for use.
- April 6, 2017: Alexion submitted revised draft labeling in BLA 125166/S-422.
- April 18, 2017: Alexion submitted a revised REMS supporting document and a response to the additional questions in the REMS assessment for a supplemental application for a new indication in BLA 125166/S-422.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Myasthenia gravis is an autoimmune disease of neuromuscular transmission that manifests in two clinical forms, ocular and generalized. The clinical hallmark of the disease is weakness in ocular, bulbar, limb, and respiratory muscles. In ocular myasthenia, weakness is limited to the eyelids and extraocular muscles, whereas the weakness in generalized myasthenia commonly affects ocular muscles as well as a variable combination of bulbar, limb, and respiratory muscles. Weakness results from an antibody-mediated, T-cell dependent immunologic attack directed at acetylcholine receptors and/or receptor-associated proteins in the postsynaptic membrane of the neuromuscular junction. Most patients with the generalized form of the disease are seropositive for antibodies. The worldwide prevalence rate of myasthenia gravis is estimated to range from 15 to 179 per million persons.[1] Use of the upper limit of that range and the current estimated U.S. population of 325 million[b] results in an overall crude U.S. prevalence estimate of approximately 58,000 persons.

Clinical symptoms of myasthenia gravis may include ocular ptosis or diplopia; bulbar symptoms such as dysarthria, dysphagia, and fatigable chewing; weakness of facial, neck, and proximal limb muscles; and respiratory muscle weakness, which is the most serious symptom. Respiratory muscle weakness may lead to respiratory insufficiency or respiratory failure, which is referred to as myasthenic crisis.

Early in the disease course, the symptoms of weakness are transient in many patients, with hours to days free of symptoms. The symptoms may even remit spontaneously for weeks or longer. The progression of myasthenia gravis usually peaks within a few years of disease onset. Although data are limited, a

[b] Accessed online at www.census.gov, June 13, 2017.

population study in Denmark found that seropositive myasthenia gravis may be associated with increased mortality.[2]

3.2 Description of Current Treatment Options

The initial treatment for most patients with myasthenia gravis is an oral acetylcholinesterase inhibitor, such as pyridostigmine, which decreases the degradation of acetylcholine in the neuromuscular junction. Acetylcholinesterase inhibitors provide marked symptomatic improvement in some patients but little or no improvement in others. Most patients eventually require immunotherapy during the course of their disease. Immunosuppressive agents such as glucocorticoids, azathioprine, mycophenolate mofetil, and cyclosporine are used as chronic treatments to bring about and maintain remission or clinical improvement, though these treatments typically take weeks to months before onset of the clinical effect. These treatments are also associated with various adverse effects, some serious. Adverse effects of glucocorticoids may include cataracts, hypertension, diabetes, and osteoporosis, among others. Azathioprine is associated with a flu-like illness as well as hepatotoxicity, cytopenias, and malignancies. The most common adverse effects of mycophenolate are gastrointestinal; leukopenia can also occur. Hypertension and nephrotoxicity are the most common limiting adverse effects of cyclosporine. In situations where a rapid onset of effect is needed, such as in severe or rapidly worsening generalized disease, the use of plasmapheresis or intravenous immune globulin may be indicated, but the duration of benefit with these rapid-acting treatments typically lasts only three to six weeks.[3,4]

4 Benefit Assessment

The pivotal clinical study (ECU-MG-301) supporting the application is a phase 3, multicenter, randomized, double-blind, placebo controlled study of eculizumab in 125 patients with refractory generalized myasthenia gravis and a positive serologic test for anti-acetylcholine receptor antibodies. Patients randomized to eculizumab received 900 mg weekly for the first month followed by maintenance doses of 1200 mg every two weeks over a period of 26 weeks. Eligible patients were vaccinated against Neisseria meningitidis if not already vaccinated according to current medical and country guidelines. Patients who completed Study MG-301 were eligible to receive eculizumab in ECU-MG-302, an open label extension study.

The primary efficacy endpoint was the change from baseline in the Myasthenia Gravis Activities of Daily Living score (MG-ADL), a patient-reported outcome that measures functional disability on a 24-point scale (higher scores indicate more severe impairment). Secondary endpoints also evaluated changes from baseline using several scales including the Quantitative Myasthenia Gravis (QMG) score, a physician-assessed measure of physical function and muscle strength; the Myasthenia Gravis Composite (MGC) score, a hybrid of physician- and patient-reported items to measure clinical status; and the 15-item Myasthenia Gravis Quality of Life (MG-QOL 15) score, a patient-reported instrument.

Analysis of the mean change from baseline in MG-ADL score at Week 26 found a greater improvement in patients who received eculizumab (-4.7) than in patients who received placebo (-2.8). The least squares mean change in worst-rank MG-ADL score from baseline to Week 26 showed a difference of -11.7 in favor of eculizumab compared with placebo (p=0.07). However, this measure was determined using a statistical

analysis plan that ranked all treatment discontinuations as worst-rank, regardless of whether discontinuation was related to clinical deterioration or not. Using a modified plan that changed the ranking for discontinuations unrelated to clinical deterioration resulted in a difference in worst-rank MG-ADL least squares mean score of -15.4 (p=0.016) in favor of eculizumab. The difference in least squares mean rank scores for each of the secondary endpoints QMG, MGC, and MG-QOL 15 were all significant in favor of eculizumab at $p<0.05$.[5,6,c]

The analysis of efficacy remains under review and the clinical team's final conclusions remain pending at this time.

5 Risk Assessment and Safe-Use Conditions

The myasthenia gravis safety population is comprised of 133 eculizumab-treated patients in controlled and open-label studies. Per section 505-1(g)(2)(A) of the FDCA, an Applicant is required to submit a REMS assessment when submitting a supplemental application for a new indication for use. Alexion concludes that the main risk of eculizumab in treating patients with (b) (4) myasthenia gravis, which is the risk of meningococcal infections, is similar to that in the other approved indications, and that the new indication does not introduce new unexpected risks. In this way, the benefit-risk profile remains the same; at this time, the DNP clinical team agrees with this conclusion.[d] Alexion also asserts the REMS modification will not introduce additional burden to prescribers and patients and would not adversely impact patient access to treatment for the (b) (4) myasthenia gravis population. DRISK agrees the modification will not create unnecessary burden on prescribers or adversely affect access to eculizumab for patients with myasthenia gravis.

5.1 Serious Adverse Events

There were two deaths in eculizumab-treated patients in the clinical development program. One case occurred in a (b) (6) female who withdrew from the study on Day 128 due to myasthenic crisis, which progressed to respiratory failure and prolonged intubation over the course of many weeks; the patient ultimately died from cardiac arrest. The second death occurred during the open label extension study in a 25 year-old female, who experienced a complicated course that included cytomegalovirus (CMV) infection, acalculous cholecystitis, hepatic failure, Acinetobacter nosocomial pneumonia, disseminated intravascular coagulopathy, renal failure, and cardiac arrest. According to the Applicant, the institution's morbidity and mortality conference proposed the cause of death as being CMV-associated hemophagocytic lymphohistiocytosis.

Overall there were 18 patients (29%) in the placebo group of Study ECU-MG-301 who experienced 33 serious adverse events (SAEs) compared with 9 (15%) patients in the eculizumab group who experienced 17 SAEs. The most commonly reported SAE in each group was myasthenia gravis (clinical worsening), which was reported in 8 (13%) placebo-treated patients and 5 (8%) eculizumab-treated patients. Serious

[c] Final study results are subject to change pending completion of the Biometrics analysis.
[d] Personal email communication, Nicholas Kozauer, DNP, August 29, 2017.

infections were reported in 6 patients in the placebo group, whereas 2 patients in the eculizumab group experienced 3 serious infections (Moraxella bacteremia and endocarditis; diverticulitis).

In the open-label extension study, SAEs were experienced by 9 (16%) patients in the placebo/eculizumab arm and 9 (16%) patients in the eculizumab/eculizumab arm. The most common SAE was myasthenia gravis (clinical worsening), which was reported in 3 (5%) patients in the placebo/eculizumab arm and 4 (7%) patients in the eculizumab/eculizumab arm. Serious infections were reported in 6 patients and included gastroenteritis, influenza, pneumonia, pseudomonal sepsis, respiratory syncytial virus infection, and tonsillitis.[7]

5.2 Severe Adverse Events

In Study ECU-MG-301, one or more severe adverse events (AEs) were experienced by 8 (13%) patients in the eculizumab group and 16 (25%) patients in the placebo group. Severe infections were reported in 2 patients in the eculizumab group (bacteremia and endocarditis; diverticulitis) and 4 patients in the placebo group. Other severe AEs that occurred in patients treated with eculizumab include myasthenia gravis, lymphopenia, intestinal perforation, pyrexia, post-procedural fistula, decreased weight, critical illness myopathy, myalgia, myasthenia gravis crisis, and atelectasis.

In Study ECU-MG-302, one or more severe AEs were experienced by 6 patients in the placebo/eculizumab arm and 9 patients in the eculizumab/eculizumab arm. The only AEs considered severe in more than one patient were myasthenia gravis (4 patients) and diarrhea (2 patients).[6]

6 Expected Postmarket Use

Eculizumab is likely to be administered in the outpatient setting in clinics and infusion centers. It is expected the prescribing community will largely be comprised of neurologists and may include other specialties such as internal medicine physicians.

7 Results of Review of Proposed REMS Modification

Changes proposed in the REMS modification are described below. Additions of text are shown with underlining and deletions as strikethrough text.[8,9]

7.1 REMS Document

Alexion proposes an editorial change to delete reference to the BLA supplement number on the first page of the document.

Reviewer comment: Alexion's proposed change is acceptable. The Agency has made a number of editorial revisions to the REMS document based on current policy, which are noted in the redlined version of the REMS document appended to this review.

7.2 REMS Materials

7.2.1 Medication Guide

The following sections of the Medication Guide were updated to align with the revised labeling:[e]

- What is Soliris? Soliris is a prescription medicine called a monoclonal antibody. Soliris is used to treat people with:
  - a disease called (b) (4) generalized Myasthenia Gravis (gMG). (b) (4) I
- How will I receive Soliris? Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes in adults…
  - (b) (4)
- What are the possible side effects of Soliris?
  Common side effects in people with (b) (4) gMG treated with Soliris include:
  - diarrhea
  - nausea
  - gastroenteritis
  - nasopharyngitis
  - upper respiratory infection
  - back pain
  - headache
  - myasthenia gravis

7.2.2 PATIENT SAFETY CARD

There are no changes proposed to the Patient Safety Card.

Reviewer comment: This is acceptable.

7.2.3 PRESCRIBER INTRODUCTORY LETTER AND ENROLLMENT FORM

Under Indications and Usage, Alexion proposes addition of the new indication:

- The treatment of patients with (b) (4) generalized Myasthenia Gravis (gMG) who are anti-Acetylcholine Receptor (AchR) antibody positive.

Under Adverse Reactions, Alexion proposes addition of the following:

- (b) (4)

Reviewer comment: The proposed changes will be acceptable providing they align with the final version of the labeling.

7.2.4 PATIENT SAFETY BROCHURE

Alexion proposes addition of the following information found at various places in the brochure:

[e] DRISK defers comment on the Medication Guide to the Division of Medical Policy Programs – Patient Labeling Team, which has responsibility for review of the Medication Guide.

- Soliris OneSource is a program offered by Alexion that provides education; assistance with funding options and access to Soliris; and ongoing treatment support for people living with PNH, (b) (4) aHUS, or gMG and their caregivers.
- Questions about PNH, aHUS, gMG or Soliris? Just call OneSource at 1.888.SOLIRIS (1.888.765.4747) to speak with an Alexion Nurse Case Manager.

The same changes as in the Medication Guide described above were incorporated into the Patient Safety Brochure (which includes a copy of the Medication Guide). However, the addition in the Patient Safety Brochure noted below contains a transposed phrase (shown in quotes) in comparison with the Medication Guide:

- (b) (4)

Reviewer comment: Although the transposed phrase does not result in a material difference, the text in the Patient Safety Brochure should duplicate the final version of the Medication Guide.

7.2.5 PRESCRIBER SAFETY BROCHURE

The same changes as in the Medication Guide described above were incorporated into the Prescriber Safety Brochure (which includes a copy of the Medication Guide). The addition noted below contains the same transposed phrase in comparison with the Medication Guide as is found in the Patient Safety Brochure:

- (b) (4) .

Reviewer comment: The Medication Guide's text in the Prescriber Safety Brochure should duplicate the final version of the Medication Guide.

The Prescriber Safety Brochure also contains a section titled Important Safety Information, which includes a list of the most frequently reported adverse reactions in the refractory gMG placebo-controlled and open label extension clinical trials.

Reviewer comment: The proposed changes will be acceptable providing they align with the final version of the labeling.

7.2.6 DOSING AND ADMINISTRATION GUIDE

Alexion proposes the following changes in various places of the Dosing and Administration Guide:

First page of the guide:

- (b) (4) .
- Dosing and Administration Guide
- Soliris is indicated for the treatment of patients with (b) (4) generalized Myasthenia Gravis (gMG) who are anti-Acetylcholine Receptor (AchR) antibody positive.

Indications and Usage:

- The treatment of patients with (b) (4) generalized Myasthenia Gravis (gMG) who are anti-Acetylcholine Receptor (AchR) antibody positive.

Adverse Reactions:

- (b) (4)

PNH Dosing Guide:

- Administer Soliris (b) (4) at the recommended dosage regimen time points, or within two days of these time points.[f]
- Dilute Soliris (b) (4) to a final admixture concentration of 5 mg/mL prior to administration.[c]

aHUS Dosing Guide:

- Administer Soliris (b) (4) at the recommended dosing interval or within 2 days before or after these time points.[c]

The supplemental dosing table for aHUS has been changed as shown below:

(b) (4) Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion

Type of Plasma Intervention	**Most Recent Soliris Dose**	**Supplemental Soliris Dose With Each (b) (4) Plasma Intervention**	**Timing of Supplemental Soliris Dose**
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	≥600 mg (b) (4) (b) (4)	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥300 mg (b) (4) (b) (4)	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

(b) (4)

Alexion proposes adding information related to the myasthenia gravis indication that is similar to the information provided for the PNH and aHUS indications as shown below:

- For patients with (b) (4) generalized Myasthenia Gravis (gMG)
  Soliris® (eculizumab) gMG Dosing Guide

[f] This proposed change was submitted under BLA 125166/S-417 but inadvertently omitted in the REMS modification approved on January 13, 2017.

All patients must be vaccinated against Neisseria meningitidis at least 2 weeks prior to the first dose of Soliris therapy. Do not initiate Soliris therapy in patients with unresolved serious Neisseria meningitidis infection or who are not currently vaccinated, unless the risks of delaying Soliris treatment outweigh the risk of developing a meningococcal infection.

Soliris is a therapy for (b) (4) gMG—a chronic disease needing chronic treatment.

Administer Soliris at the recommended dosing interval or within 2 days before or after these time points.

Please see enclosed full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infection.

Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion

Type of Plasma Intervention	**Most Recent Soliris Dose**	**Supplemental Soliris Dose With Each Plasma Intervention**	**Timing of Supplemental Soliris Dose**
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	≥600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥300 mg	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

Monitoring after Discontinuation

Use of Soliris in (b) (4) gMG treatment has been studied only in the setting of chronic administration.

Discontinuation of Soliris should only be considered if medically justified. Stopping Soliris treatment in this disease characterized by uncontrolled terminal complement activation may expose patients to the risk of substantial disease worsening and/or deterioration of MG symptoms.

Preparation for Administration:

(b) (4)

Reviewer comment: The proposed changes will be acceptable provided they align with the final version of the labeling.

7.2.7 REMS WEBSITE

There are no changes proposed to the REMS website.

Reviewer comment: This is acceptable as there are no indication-specific sections of the REMS website.

7.3 REMS SUPPORTING DOCUMENT AND ASSESSMENT PLAN

A summary of pertinent revisions that Alexion made to the REMS supporting document are outlined in Table 1.[10] Revisions related to changes already described in Sections 7.1 and 7.2 above are not repeated in Table 1.

Table 1. Applicant's proposed revisions to the REMS supporting document.

Page(s)*	Revision	Reviewer Comment
3	Revised the email address for prescribers to send the completed prescriber enrollment form to OSSP@alexion.com	This revision is not consistent with the REMS document, which shows the email address to be OSSP@alxn.com.
14	Inserted an explanation for the early submission of the REMS assessment report scheduled on June 1, 2017 as part of the myasthenia gravis efficacy supplement submission.	Acceptable
18-19	Revised the REMS assessment plan to be consistent with the REMS Assessment Plan Revision letter sent by the Agency on September 15, 2015.	Acceptable
20	Revised distribution of the Medication Guide to delete reference to the One Source Support Program as well as Soliris Specialists as means of providing additional copies of the Medication Guide at the time of voluntary patient enrollment or at other times.	Acceptable
22	Clarified that the OneSource Support Program is responsible for activities related to voluntary patient enrollment but adverse event reports are to be submitted to Alexion.	Acceptable. DRISK does not find a material difference in concept.

* Redlined version of supporting document submitted to BLA 125166 (Seq. 586) on April 18, 2017.

Reviewer comment: The supporting document provides no details on the REMS compliance plan currently in use, and states, "Based on monitoring and evaluation of the Elements to Assure Safe Use, Alexion will take reasonable steps to improve the compliance with the implementation of these elements as needed. If a prescriber is found to be non-compliant, Alexion will take the appropriate measures to support the practitioner and gain compliance with the program." In considering the expected increase in size of the prescribing population, DRISK requests additional details that describe the process of identifying and correcting non-compliance.

REMS Assessment Plan[9]

Alexion proposes no changes to the current REMS assessment plan and states no additional evaluations are anticipated for the myasthenia gravis indication.

Reviewer comment: In considering the addition of a new group of prescribers and patients, DRISK requests an assessment of prescriber and patient understanding regarding the safe use of Soliris for the treatment of myasthenia gravis through the use of survey methods.

Additionally, the DRISK review (pending) of the 7-Year REMS Assessment Report submitted to BLA 125166 on December 23, 2016 and May 26, 2017 finds that the prescriber and patient surveys previously discontinued for the PNH and aHUS indications are to be reinstated. This is necessary to fully assess whether or not the REMS is meeting the second goal of the REMS and is due in part to recent changes to the Advisory Committee on Immunization Practices (ACIP) meningococcal immunization recommendations

as well as other concerns related to the most recent REMS assessment report.[g] The timetable for submission of assessments is to remain every two years as stated in the currently approved REMS.

8 Discussion

Alexion has proposed a REMS modification for eculizumab as part of a supplemental application for a new indication for the treatment of (b) (4) . The modification proposes changes to the REMS appended materials to align with labeling changes related to the new indication and makes corrections to the REMS supporting document that are largely editorial in nature.

It appears that adequate evidence of clinical efficacy has been established for the use of eculizumab for the treatment of adult patients with myasthenia gravis who are anti-acetylcholine receptor (AchR) antibody positive, though the supplemental application remains under review and the clinical team's final conclusions related to the evidence of efficacy are pending at this time.

Myasthenia gravis is an autoimmune disease of neuromuscular transmission that can result in disability and serious morbidity, including respiratory muscle weakness that can lead to respiratory insufficiency and respiratory failure. The pivotal study's primary efficacy endpoint of change from baseline in the MG-ADL total score at week 26 as measured by a worst-rank analysis found a difference in least squares mean score of -15.4 (p=0.016) in favor of eculizumab. The secondary endpoints also showed a significant difference in favor of eculizumab. The final study results are pending completion of the Biometrics analysis.

Based on the drug's mechanism of action the most serious risk of eculizumab in treating myasthenia gravis is that of meningococcal infection, which requires a REMS with ETASU for the currently approved PNH and aHUS indications. Additional risks include other serious infections, particularly with encapsulated organisms; disease worsening upon discontinuation of treatment; and the potential for hypersensitivity or infusion reactions, which is an inherent risk with monoclonal antibody infusions.

Since the risk of invasive meningococcal infection for the treatment of myasthenia gravis is the same for myasthenia gravis as in the already-approved indications, it is necessary to modify the REMS to account for the new indication and thereby incorporate the REMS as part of the supplemental application approval. Alexion proposes modifications to the appended materials to align with the related labeling changes. The modifications to the REMS materials will be acceptable provided they are accurately aligned with the final version of the labeling; this may require submission of amended materials, as the labeling remains under review at this time and is subject to change.

The Applicant did not propose any revision to the REMS assessment plan. However, in considering the addition of a new group of eculizumab prescribers and patients, an assessment of prescriber and patient understanding regarding the safe use of eculizumab for the treatment of myasthenia gravis seems reasonable. Additionally, DRISK finds the prescriber and patient surveys are to be reinstated for the PNH

[g] Personal email communication, Igor Cerny, DRISK, August 12, 2017.

and aHUS indications; this in part is due to recent changes to the ACIP's meningococcal immunization recommendations, as well as other concerns related to the most recent REMS assessment report. The Applicant will need to submit a new survey methodology protocol for review prior to starting the surveys. DRISK also notes the REMS supporting document provides no details on the REMS compliance plan currently in use. Inasmuch as the size of the prescribing population is expected to increase, DRISK requests additional details that describe the process of identifying and correcting non-compliance with the REMS. DRISK has prepared comments regarding the proposed modification for Alexion to address as described below.

9 Recommendations

We recommend that the comments in Section 10 be sent to Alexion in an Information Request. In addition, include a request that the Applicant submit their response within 10 business days and to reply by email with the anticipated date of resubmission upon receipt of this correspondence.

10 Comments to the Applicant

We are providing these comments to you before we complete our review of the entire supplemental application to give you notice of issues that we have identified in the proposed REMS modification submitted under BLA 125166/S-422. We ask Alexion to submit a response to these comments within 10 business days to facilitate further review, and to reply by email with the anticipated date of resubmission upon receipt of this correspondence.

1. REMS Document
   Based on current policy, the Agency has made a number of editorial revisions to the REMS document, which are noted in the redlined version of the REMS document attached to this correspondence.
2. REMS Supporting Document and REMS Assessment Plan
   a. We note the email address for prescribers to send the completed prescriber enrollment form to OSSP@alexion.com is not consistent with the REMS document, which shows the email address to be OSSP@alxn.com.
   b. The REMS supporting document provides no details on the REMS compliance plan currently in use and states, "Based on monitoring and evaluation of the Elements to Assure Safe Use, Alexion will take reasonable steps to improve the compliance with the implementation of these elements as needed. If a prescriber is found to be non-compliant, Alexion will take the appropriate measures to support the practitioner and gain compliance with the program." In considering the expected increase in size of the prescribing population, we request additional details that describe the process of identifying and correcting non-compliance be added under Section 4 of the REMS supporting document.
3. As there will be new groups of prescribers and patients who will be impacted by the REMS, we request an assessment of prescriber and patient understanding regarding the safe use of Soliris for the treatment of myasthenia gravis through the use of similar methods as previously conducted for the PNH and aHUS populations. Additionally, the prescriber and patient surveys previously

discontinued for the PNH and aHUS indications are to be reinstated. This is necessary to fully assess whether or not the REMS is meeting the second goal of the REMS and is due in part to recent changes to the Advisory Committee on Immunization Practices (ACIP) meningococcal immunization recommendations. You will need to submit a new survey methodology protocol for review at least 90 days before starting the surveys.

4. You are proposing modifications to several materials appended to the REMS including the Medication Guide, Prescriber Introductory Letter and Enrollment Form, Patient Safety Brochure, Prescriber Safety Brochure, and the Dosing and Administration Guide. The proposed modifications will need to reflect and align with the final FDA-approved product labeling, should the Agency ultimately approve supplement-422. If the modifications currently proposed do not reflect and align with the final FDA-approved labeling, you will be notified to submit amended REMS materials as part of a REMS amendment in order for the REMS modification to be approved.

At this time, please submit both a tracked changes version and a clean version of the REMS supporting document, and provide a cover letter explaining all comments and proposed changes.

We remind you that the labeling, REMS document, REMS appended materials, and REMS supporting document must all be aligned.

11 Appendix

11.1 References

[1] Carr AS, et al. A systematic review of population based epidemiological studies in myasthenia gravis. BMC Neurol 2010; 10:46.

[2] Bird SJ. Clinical manifestations of myasthenia gravis. In:UpToDate, Shefner JM, Targoff IN, Dashe JF (Eds), UpToDate, Waltham, MA 2017.

[3] Bird SJ. Treatment of myasthenia gravis. In:UpToDate, Shefner JM, Targoff IN, Dashe JF (Eds), UpToDate, Waltham, MA 2017.

[4] Bird SJ. Chronic immunomodulating therapies for myasthenia gravis. In:UpToDate, Shefner JM, Targoff IN, Dashe JF (Eds), UpToDate, Waltham, MA 2017.

[5] Alexion. Clinical Overview for eculizumab, BLA 125166 S-422, December 23, 2016.

[6] Alexion. Summary of Clinical Efficacy for eculizumab, BLA 125166 S-422, December 23, 2016.

[7] Alexion. Summary of Clinical Safety for eculizumab, BLA 125166 S-422, December 23, 2016.

[8] Alexion. REMS Modification for eculizumab, BLA 125166 S-422, December 23, 2016.

[9] Alexion. Proposed Labeling, BLA 125166 S-422, April 6, 2017.

[10] Alexion. REMS Correspondence, Response to Information Request, BLA 125166 S-422, April 18, 2017.

4 Page(s) of Draft REMS Witheld in Full as b4(CCI/TS) Immediately Following this Page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT G PRATT
08/31/2017

JAMIE C WILKINS PARKER
08/31/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166Orig1s422

Administrative/Correspondence Document(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101219

MEETING MINUTES

Alexion Pharmaceuticals, Inc.
Attention: Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
352 Knotter Drive
Cheshire, CT 06410

Dear Ms. Lyons:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for eculizumab.

We also refer to the telecon between representatives of your firm and the FDA on March 20, 2013. The purpose of the meeting was to discuss the overall proposed development plan of eculizumab as a potential treatment for generalized myasthenia gravis.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF TELECON MINUTES

Meeting Type:	**Type B**
Meeting Category:	**End-of-Phase 2**
Meeting Date and Time:	March 20, 2013 9:00 A.M. EST
Meeting Location:	FDA White Oak Campus, Building 22, Rm. 4270
Application Number:	IND 101219
Product Name:	Eculizumab (h5G1.1-mAB)
Indication:	Generalized myasthenia gravis
Sponsor/Applicant Name:	Alexion Pharmaceuticals, Inc.
Meeting Chair:	Russell G. Katz, M.D.

FDA ATTENDEES

Center for Drug Evaluation and Research
Robert Temple, MD, Deputy Director for Clinical Science

Division of Neurology Products
Russell Katz, MD, Director
Eric Bastings, MD, Deputy Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Andrew Sostek, PhD, Clinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager

Office of Clinical Pharmacology
Angela Men, MD, PhD, Clinical Pharmacology Team Leader
Xinning Yang, PhD, Clinical Pharmacology Reviewer
Satjit Brar, PhD, Pharmacometric Reviewer

Division of Monoclonal Antibodies, Office of Biotechnology Products
Lixin Xu, MD, PhD, Product Quality Reviewer

Division of Biometrics I
Kun Jin, PhD, Biometrics Team Leader

Office of Surveillance and Epidemiology
Irene Z. Chan, PharmD, BCPS, Team Leader, Division of Med Error Prevention & Analysis
Julie Neshiewat, PharmD, Safety Reviewer, DMEPA
Cindy Kortepeter, PharmD, Team Leader, Division of Pharmacovigilance

SPONSOR ATTENDEES

Alexion Pharmaceuticals
Camille L. Bedrosian, MD, Senior Vice President, Chief Medical Officer
Warren Wasiewski, MD, Vice President, Clinical Development, Neurology
Howard Yuwen, PhD, Executive Director Regulatory, US & Canada
Fanny O'Brien, PhD, Senior Director of Biostatistics
Jing Wang, MD, Associate Medical Director
Elizabeth Sullivan, Director, Global Project Management
Mary F. Lyons, RAC, Senior Manager, Regulatory Affairs
Chetan Lathia, PhD, Executive Director, Clinical Pharmacology

1.0 BACKGROUND

Alexion Pharmaceuticals has initiated a clinical development program for eculizumab in the treatment of (b) (4) generalized myasthenia gravis (gMG), defined as patients who have failed prior immunosuppressant therapy or who have required chronic IVIg or plasma exchange to control their disease. Eculizumab is a humanized monoclonal antibody directed against the human complement component C5.

The purpose of this meeting is to discuss the overall development plan and the proposed design of the Phase III trial, which is the sponsor's planned pivotal clinical trial to support registration of eculizumab for the treatment of patients with gMG.

2. DISCUSSION

Question 1:

On March 3, 2008, the Division of Neurology Products provided preliminary comments to Alexion's pre-IND briefmg package for eculizumab as a treatment for generalized myasthenia gravis where the Division indicated that ordinarily at least 2 randomized placebo-controlled studies are required to support a licensing application. Given the fact that (b) (4) generalized MG is a rare disorder and that eculizumab is being developed for treatment of (b) (4) generalized MG as a new indication, does the agency agree that a single adequate and well-controlled multicenter clinical trial that is designed following the principle as outlined in the 1998 FDA *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* that generates consistent treatment response and persuasive statistical significance, is adequate to support registration for eculizumab for the new indication in (b) (4) generalized MG?

FDA Preliminary Response to Question 1:

Yes.

Meeting Discussion:

There was no discussion.

Question 2:

Alexion believes that a statistically significant result in changes of (b) (4) score will translate into a clinically meaningful benefit to patients with (b) (4) generalized MG, and (b)(4) . Does the agency agree?

FDA Preliminary Response to Question 2:

Because the signs of myasthenia are measured by the [redacted] during clinical maneuvers [redacted], it is not clear that improvement on the following items on [redacted] would correlate to clinically meaningful improvement: [redacted]. These items therefore should not be included if [redacted] is used as the primary endpoint, or the items should revised in such a way that an improvement would clearly reflect clinical benefit. For example, [redacted] is clinically meaningful, and improvement to [redacted] would reflect clinically meaningful improvement.

Even without the above three items, there is the potential that a small yet statistically significant improvement in score might correspond to little if any clinical improvement perceptible to the patient. This possibility is particularly problematic for eculizumab because the drug is associated with serious risks, and you must not only demonstrate that the drug has benefit to patients in their daily lives, but in addition that the benefit-risk profile is acceptable in gMG. Improvement on a more clearly clinically meaningful endpoint, perhaps like MG Activity of Daily Living Profile, might be preferable as a primary or co-primary endpoint. We would be open to discussion of other endpoints, or additional modification [redacted] increase confidence that improvement would reflect clinical perceptible benefit.

Your proposal to consider [redacted] taking into consideration a secondary endpoint representing [redacted] symptoms is problematic because [redacted] is not well-defined.

Meeting Discussion:

The sponsor began by outlining the previous regulatory history of the drug. They noted that it had been approved for 6 years for two indications and with [redacted] patient-year's exposure, including infants. The sponsor noted that the safety profile was well known and that the risk of infections was 0.5% per 100 patient-years of exposure.

While acknowledging the Division's concerns about the items in the [redacted] that reflected clinical signs, not symptoms, they asserted that [redacted] combined with the [redacted] would provide a reliable measure of clinically meaningful improvement. The Division emphasized that using the [redacted] was problematic because such a designation has no clear regulatory interpretation. The Division suggested the ADL might be preferable as a primary or co-primary endpoint (similarly to the global assessment in Alzheimer's disease that is used as a co-primary endpoint with a measure of cognitive function).

The sponsor asserted that their demonstration in a small study of a large beneficial effect indicated that the drug effect [redacted] was likely to be clinically meaningful. The Division pointed out that in the phase 3 trial the effect size might not be as large, and

even though the study was powered based on a [redacted](b)(4) *the study might be positive even if the effect* [redacted](b)(4) *was smaller. Also, the clinical meaningfulness of any given* [redacted](b)(4) *depend on the specific items for which change occurred, complicating interpretation.*

The Division further noted that for a single adequate and well-controlled study to be used to support efficacy the effect must be robust, including having consistent effects across multiple independent endpoints.

The Division discussed the possibility of designing a trial with outcomes calibrated to individual MG patient's particular problems. For example, MG patients with mainly breathing difficulties could have an outcome measuring breathing, while patients with mainly walking difficulties could have an outcome measuring walking. Various advantages of this strategy were discussed, such as need for fewer patients and decreased variability. These patient groups could be stratified at randomization. The sponsor could employ individually calibrated scales for different patients, noting that all endpoints must be pre-specified.

The Company asked if the ADL endpoint would be reviewed by the Study Endpoint and Labeling Development (SEALD) team. The Division indicated that would not be necessary for the Division to accept the endpoint.

The sponsor asked if the ADL could be used as a stand-alone primary endpoint (i.e. not as a co-primary endpoint). The Division confirmed it would be acceptable.

Question 3:

Does the Agency agree that the clinical assessments outlined in the synopsis are sufficient to demonstrate efficacy of eculizumab also in the treatment of patients with [redacted](b)(4)?

FDA Preliminary Response to Question 3:

To support approval you need to show that patients benefit from eculizumab on a [redacted](b)(4)

Meeting Discussion:

See discussion under question 2.

Question 4:

The demonstration of safety and efficacy supporting the use of eculizumab in the treatment of (b) (4) gMG will be based on a 26-week double-blind placebo-controlled study (b)(4) patients randomized (b)(4) Does the Agency agree?

FDA Preliminary Response to Question 4:

Adequate characterization of the risks of eculizumab in gMG is necessary for approval. The safety database upon which eculizumab was approved for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome was small, and the risks to gMG patients might differ from previously studied patients. It is not clear how much safety information would be available from other indications in which eculizumab has been studied but for which it is not yet approved. After the 26-week double-blind period, are you planning on an open-label extension?

Meeting Discussion:

The sponsor confirmed that they are planning an open-label extension.

Question 5:

Does the Agency agree that the proposed patient selection criteria based on failure of prior immunosuppressant therapy or a requirement for chronic use IVIg or plasma exchange to maintain clinical stability are adequate to support the registration of eculizumab in patients with (b) (4) generalized MG ?

FDA Preliminary Response to Question 5:

The appropriate selection criteria depend in part on the primary endpoint selected, and the method of analysis. (b)(4) This appears problematic for both interpretable efficacy evaluation and adequate protection of patient safety. It is likely that the study can be revised so that it appropriately (b)(4), but it is not clear to us from the description provided in the briefing book that this is currently the case.

Meeting Discussion:

The Division thought the patient selection criteria could be acceptable, but the sponsor would have to consider when selecting patients (b)(4) (b)(4)

Question 6:

The proposed dosing regimen is 900 mg for 4 weeks followed by 1200 mg for the 5th dose and then every two weeks. This dose will be evaluated in the planned Phase III clinical trial. Does the Agency agree with the proposed dosing regimen for the planned Phase III clinical trial for the treatment of (b) (4) generalized MG?

FDA Preliminary Response to Question 6:

Based on the supplied information, the proposed dosing regimen is acceptable. We recommend you also collect samples on Visit 6 (Week 4) and Follow-up Visit (4 weeks after the end of treatment) for evaluation of serum human anti-human antibodies in order to better characterize the immunogenicity in the indicated population.

Meeting Discussion:

The sponsor acknowledged the comment and agreed to amend the protocol to add the immunogenicity sampling.

3.0 ADDITIONAL COMMENTS

3.1 PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 16, 2012. If an EOP2 meeting occurred prior to November 16, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm04

9867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email CDER PMHS@fda.hhs.gov .

3.2 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
04/19/2013