CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125166s431

Trade Name: SOLIRIS

Generic or Proper Name: eculizumab

Sponsor: Alexion Pharmaceuticals, Inc.

Approval Date: June 27, 2019

Indication:

Soliris is a complement inhibitor indicated for:

- 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.

- 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 generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive.
- The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive (1.4).

CENTER FOR DRUG EVALUATION AND RESEARCH

125166s431

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APPLICATION NUMBER:

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APPROVAL LETTER

BLA 125166/S-431

SUPPLEMENT APPROVAL

Alexion Pharmaceuticals, Inc.
Attention: Michael Page
Executive Director, Global Regulatory Affairs
121 Seaport Boulevard
Boston, MA 02210

Dear Mr. Page:

Please refer to your supplemental biologics license application (sBLA), dated and received December 28, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Soliris (eculizumab).

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated May 28, 2019.

This Prior Approval sBLA provides for the use of Soliris for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive and for proposed modifications to the approved REMS.

APPROVAL & LABELING

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

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 FDA.gov,[1] 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.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

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 Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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

CARTON AND CONTAINER LABELS

We acknowledge your December 28, 2018, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 (REMS) REQUIREMENTS

The REMS for Soliris was originally approved on June 4, 2010, and the most recent modification was approved on July 25, 2018. The REMS consists of elements to assure safe use and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of changes to the Prescriber Safety Brochure to align with labeling changes related to the new indication and to align with revised wording in

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

the Indications and Usage section of labeling related to the generalized myasthenia gravis indication.

Your proposed modified REMS, submitted on December 28, 2018, amended 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 July 25, 2018, 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 that 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 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

or

NEW SUPPLEMENT FOR BLA 125166/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125166/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125166/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125166/ S-000
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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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 *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

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 FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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, call LCDR Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labels
- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM H Dunn
06/27/2019 12:04:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166s431

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.)**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. 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 (5.1).

RECENT MAJOR CHANGES

Indications and Usage (1.4)	06/2019
Dosage and Administration (2.4, 2.5)	06/2019
Dosage and Administration (2.5, 2.6, 2.7)	07/2018
Warnings and Precautions (5.1, 5.2)	07/2018

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 generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive (1.3).
- The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive (1.4).

DOSAGE AND ADMINISTRATION

For intravenous infusion only
PNH Dosage Regimen: (2.2)
aHUS Dosage Regimen: (2.3)
gMG and NMOSD Dosage Regimen: (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/30 mL (10 mg/mL) in a 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 (5.1).
- 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).

The most frequently reported adverse reactions in the NMOSD placebo-controlled trial (≥10%) are: upper respiratory infection, nasopharyngitis, diarrhea, back pain, dizziness, influenza, arthralgia, pharyngitis, and contusion (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.

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2019

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].**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. 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 (5.1)*]. 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 generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive.

1.4 Neuromyelitis Optica Spectrum Disorder (NMOSD)

Soliris is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Vaccination and Prophylaxis

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

Provide two weeks of antibacterial drug prophylaxis to patients if Soliris must be initiated immediately and vaccines are administered less than two weeks before starting Soliris therapy.

Healthcare professionals who prescribe Soliris must enroll in the Soliris REMS [*see Warnings and Precautions (5.1)*].

2.2 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)*].

2.3 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 aHUS 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.

2.4 Recommended Dosage Regimen – gMG and NMOSD

For adult patients with generalized myasthenia gravis or neuromyelitis optica spectrum disorder, 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.

2.5 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 or NMOSD, 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	Within 60 minutes after each

		plasma exchange session	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

2.6 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.

2.7 Administration

Only administer as an intravenous infusion.

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/30 mL (10 mg/mL) as a clear, colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection [*see Warnings and Precautions (5.1)*].
- 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

Risk and Prevention

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). Soliris is associated with an approximate 2,000-fold increased risk of meningococcal disease in comparison to the general U.S. population annual rate (0.14 per 100,000 population in 2015).

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 and provide patients with two weeks of antibacterial drug prophylaxis.

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.

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.

5.2 Other Infections

Serious infections with *Neisseria* species (other than *N. meningitidis*), including disseminated gonococcal infections, have been reported.

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 influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* 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)*].

5.3 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.

5.4 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.

5.5 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 (5.2)*]
- Monitoring Disease Manifestations after Soliris Discontinuation [*see Warnings and Precautions (5.3)*]
- Thrombosis Prevention and Management [*see Warnings and Precautions (5.4)*]

- Infusion Reactions [*see Warnings and Precautions (5.5)*]

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 aHUS in Studies C08-002A/B, C08-003A/B and C10-004. All 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 C10-004 Separately 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 (15)	8 (20)	17 (22)
Gastrointestinal Disorders				

	Number (%) of Patients			
	C08-002A/B (N=17)	**C08-003A/B (N=20)**	**C10-004 (N=41)**	**Total (N=78)**
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				
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 Study C10-003

	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 C09-001r included 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)
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				

	Number (%) of Patients			
	< 2 yrs (N=5)	2 to < 12 yrs (N=10)	12 to <18 yrs (N=4)	Total (N=19)
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 [*see Clinical Studies (14.3)*]. 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 on 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

	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)

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, and that are not included in Table 8 were headache (26%), nasopharyngitis (24%), diarrhea (15%), arthralgia (12%), upper respiratory tract infection (11%), and nausea (10%).

Neuromyelitis Optica Spectrum Disorder (NMOSD)

In a placebo-controlled trial evaluating the effect of Soliris for the treatment of NMOSD (NMOSD Study 1), 96 patients received Soliris at the recommended dosage regimen and 47 patients received placebo [*see Clinical Studies (14.4)*]. Patients were 19 to 75 years of age (mean 44 years of age), and 91% were female. Table 9 displays the most common adverse reactions from NMOSD Study 1 that occurred in ≥5% of Soliris-treated patients and at a greater frequency than on placebo.

Table 9: Adverse Reactions Reported in 5% or More of Soliris-Treated Patients in NMOSD Study 1 and at a Greater Frequency than in Placebo-Treated Patients

	Soliris (N=96) N (%)	**Placebo (N=47) N (%)**
Events/Patients	1295/88	617/45
Blood and lymphatic system disorders		
Leukopenia	5 (5)	1 (2)
Lymphopenia	5 (5)	0 (0)
Eye disorders		
Cataract	6 (6)	2 (4)

	Soliris (N=96) N (%)	Placebo (N=47) N (%)
Gastrointestinal disorders		
Diarrhea	15 (16)	7 (15)
Constipation	9 (9)	3 (6)
General disorders and administration site conditions		
Asthenia	5 (5)	1 (2)
Infections and infestations		
Upper respiratory tract infection	28 (29)	6 (13)
Nasopharyngitis	20 (21)	9 (19)
Influenza	11 (11)	2 (4)
Pharyngitis	10 (10)	3 (6)
Bronchitis	9 (9)	3 (6)
Conjunctivitis	9 (9)	4 (9)
Cystitis	8 (8)	1 (2)
Hordeolum	7 (7)	0 (0)
Sinusitis	6 (6)	0 (0)
Cellulitis	5 (5)	1 (2)
Injury, poisoning and procedural complications		
Contusion	10 (10)	2 (4)
Metabolism and nutrition disorders		
Decreased appetite	5 (5)	1 (2)
Musculoskeletal and connective tissue disorders		
Back pain	14 (15)	6 (13)

	Soliris (N=96) N (%)	Placebo (N=47) N (%)
Arthralgia	11 (11)	5 (11)
Musculoskeletal pain	6 (6)	0 (0)
Muscle spasms	5 (5)	2 (4)
Nervous system disorders		
Dizziness	14 (15)	6 (13)
Paraesthesia	8 (8)	3 (6)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	7 (7)	2 (4)
Skin and subcutaneous tissue disorders		
Alopecia	5 (5)	2 (4)

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, gMG, and NMOSD indications, 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. None of the 62 patients with gMG had antibodies to Soliris detected following the 26-week active treatment. Two of the 96 (2%) Soliris-treated patients with NMOSD had antibodies to Soliris detected during the entire treatment period.

An ECL based neutralizing assay with a low sensitivity of 2 mcg/mL was performed to detect neutralizing antibodies for the 5 patients with PNH, the 3 patients with aHUS, and the 2 patients with NMOSD with anti-eculizumab antibody positive samples using the ECL assay. Two of 161 patients with PNH (1.2%) and 1 of 100 patients with aHUS (1%), and none of the 96 patients with NMOSD had low positive values for neutralizing antibodies.

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.

Fatal or serious infections: *Neisseria gonorrhoeae, Neisseria meningitidis, Neisseria sicca/subflava, Neisseria spp* unspecified

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data on outcomes of pregnancies that have occurred following Soliris use in pregnant women have not identified a concern for specific adverse developmental outcomes (*see Data*). There are risks to the mother and fetus associated with untreated paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) in pregnancy (*see Clinical Considerations*). 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 (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or fetal/neonatal risk

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, and adverse fetal outcomes, including fetal death and premature delivery.

aHUS in pregnancy is associated with adverse maternal outcomes, including pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including intrauterine growth restriction (IUGR), fetal death and low birth weight.

Data

Human Data

A pooled analysis of prospectively (50.3%) and retrospectively (49.7%) collected data in more than 300 pregnant women with live births following exposure to Soliris have not suggested safety concerns. However, these data cannot definitively exclude any drug-associated risk during pregnancy, because of the limited sample size.

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

Although limited published data does not report detectable levels of eculizumab in human milk, maternal IgG is known to be present in human milk. Available information is insufficient to inform the effect of eculizumab on the breastfed infant. There are no data on the effects of eculizumab on milk production. 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 eculizumab or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of Soliris for the treatment of PNH, gMG, or NMOSD 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)*].

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

8.5 Geriatric Use

Fifty-one patients 65 years of age or older (15 with PNH, 4 with aHUS, 26 with gMG, and 6 with NMOSD) 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

Eculizumab, a complement inhibitor, 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 (eculizumab) injection 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 30 mL vial contains 300 mg of eculizumab, polysorbate 80 (6.6 mg) (vegetable origin), sodium chloride (263.1 mg), sodium phosphate dibasic (53.4 mg), sodium phosphate monobasic (13.8 mg), 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.

The precise mechanism by which eculizumab exerts its therapeutic effect in NMOSD is unknown, but is presumed to involve inhibition of aquaporin-4-antibody induced terminal complement C5b-9 deposition.

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, gMG, and NMOSD, 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. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with NMOSD, at week 24, the observed mean±SD Cmax was 877±331 and the Ctrough was 429±188 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 414 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 (2.5)*].

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).

Drug Interactions

Intravenous immunoglobulin (IVIg) treatment may interfere with the endosomal neonatal Fc receptor (FcRn) recycling mechanism of monoclonal antibodies such as eculizumab and thereby decrease serum eculizumab concentrations. Drug interaction studies have not been conducted with eculizumab in patients treated with IVIg.

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 10).

Table 10: PNH Study1 Patient Baseline Characteristics

	Study 1	
Parameter	**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)

Parameter	Study 1 Placebo (N=44)	Study 1 Soliris (N=43)
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 11). 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 11: PNH Study 1 Results

	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 (2.3)*]. 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 ≤150 x 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 12 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C08-002A/B.

Table 12: 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 (× 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 13 summarizes the efficacy results for Study C08-002A/B.

Table 13: Efficacy Results for Study C08-002A/B

Efficacy Parameter	Study C08-002A/B at 26 wks[1] (N=17)	Study C08-002A/B at 2 yrs[2] (N=17)
Complete TMA response, n (%) Median Duration of complete TMA response, weeks (range)	11 (65) 38 (25, 56)	13 (77) 99 (25, 139)
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 14 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C08-003A/B.

Table 14: 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 15 summarizes the efficacy results for Study C08-003A/B.

Table 15: Efficacy Results for Study C08-003A/B

Efficacy Parameter	Study C08-003A/B at 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 16). No pediatric patient required new dialysis during treatment with Soliris.

Table 16: Efficacy Results in Pediatric Patients Enrolled in Study C09-001r

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 On eculizumab treatment	 1 (0, 2) <1 (0, <1)	<1 (0.07, 1.46) 0 (0, <1)	 <1 (0, 1) 0 (0, <1)	 0.31 (0.00, 2.38) 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 17 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-004.

Table 17: 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. In 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 18 summarizes the efficacy results for Study C10-004.

Table 18: Efficacy Results for Study C10-004

Efficacy Parameter	Study C10-004 (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/1.73m^2, 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 C10-003 were 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 19 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-003.

Table 19: Baseline Characteristics of Patients Enrolled in Study C10-003

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 20 summarizes the efficacy results for Study C10-003.

Table 20: 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, multi-center 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 (2.4)*].

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 1 are shown in Table 21.

Table 21: 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.

14.4 Neuromyelitis Optica Spectrum Disorder (NMOSD)

The efficacy of Soliris for the treatment of NMOSD was established in NMOSD Study 1 (NCT01892345), a randomized, double-blind, placebo-controlled trial that enrolled 143 patients with NMOSD who were anti-AQP4 antibody positive and met the following criteria at screening:

1. History of at least 2 relapses in last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months prior to screening,
2. Expanded Disability Status Scale (EDSS) score ≤ 7 (consistent with the presence of at least limited ambulation with aid),
3. If on immunosuppressive therapy (IST), on a stable dose regimen,

4. The use of concurrent corticosteroids was limited to 20 mg per day or less,
5. Patients were excluded if they had been treated with rituximab or mitoxantrone within 3 months or with IVIg within 3 weeks prior to screening.

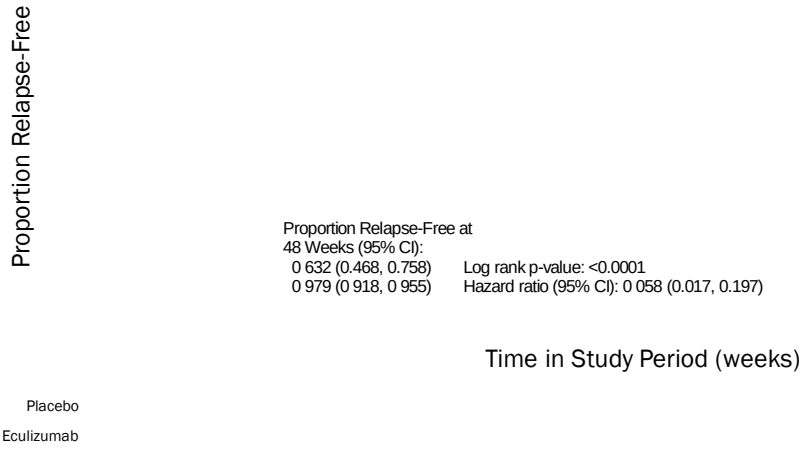
A total of 96 patients were randomized to receive Soliris treatment and 47 were randomized to receive placebo.

The baseline demographic and disease characteristics were balanced between treatment groups. During the treatment phase of the trial, 76% percent of patients received concomitant IST, including chronic corticosteroids; 24% of patients did not receive concomitant IST or chronic corticosteroids during the treatment phase of the trial.

Soliris was administered according to the recommended dosage regimen [*see Dosage and Administration (2.4)*].

The primary endpoint for NMOSD Study 1 was the time to the first adjudicated on-trial relapse. The time to the first adjudicated on-trial relapse was significantly longer in Soliris-treated patients compared to placebo-treated patients (relative risk reduction 94%; hazard ratio 0.058; $p < 0.0001$) (Figure 1).

Figure 1: Kaplan-Meier Survival Estimates for Time to First Adjudicated On-Trial Relapse – Full Analysis Set



Note: Patients who did not experience an adjudicated on-trial relapse were censored at the end of the study period. Abbreviations: CI = confidence interval

Soliris-treated patients experienced similar improvement in time to first adjudicated on-trial relapse with or without concomitant treatment. Soliris-treated patients had a 96% relative reduction in the adjudicated on-trial annualized relapse rate (ARR) compared to patients on placebo, as shown in Table 22.

Table 22: Adjudicated On-trial Annualized Relapse Rate – Full Analysis Set

Variable	Statistic	Placebo (N=47)	Soliris (N=96)
Total number of relapses	Sum	21	3
Adjusted adjudicated ARR[a]	Rate	0.350	0.016
Treatment effect[a]	Rate ratio (eculizumab/placebo)	…	0.045
	p-value	…	<0.0001

[a] Based on a Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to screening.
ARR = annualized relapse rate

Compared to placebo-treated patients, Soliris-treated patients had reduced annualized rates of hospitalizations (0.04 for Soliris versus 0.31 for placebo), of corticosteroid administrations to treat acute relapses (0.07 for Soliris versus 0.42 for placebo), and of plasma exchange treatments (0.02 for Soliris versus 0.19 for placebo).

16 HOW SUPPLIED/STORAGE AND HANDLING

Soliris (eculizumab) injection is a sterile, preservative-free, clear, colorless solution supplied as one 300 mg/30 mL (10 mg/mL) single-dose vial per carton (NDC 25682-001-01).

Store Soliris vials refrigerated at 2º-8º C (36º-46º F) in the original carton to protect from light until time of use. Soliris vials may be stored 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.

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

Counsel patients about gonorrhea prevention and advise regular testing for patients at-risk.

Inform patients that there may be an increased risk of other types of infections, particularly those due to encapsulated bacteria.

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 influenzae* 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.
121 Seaport Boulevard
Boston, MA 02210 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, US Patent No. 9,732,149 and US Patent No.9,718,880 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 if you have not already had this vaccine.

2. If your doctor decided that urgent treatment with SOLIRIS is needed, you should receive meningococcal vaccination as soon as possible.

3. If you have not been vaccinated and SOLIRIS therapy must be initiated immediately, you should also receive two weeks of antibiotics with your vaccinations.

4. 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.

5. Meningococcal vaccines reduce the risk of meningococcal infection but 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:

- o headache with nausea or vomiting
- o headache with a stiff neck or stiff back
- o fever and a rash
- o muscle aches with flu-like symptoms
- o headache and fever
- o fever
- o confusion
- o 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 the meningococcal vaccine and, if needed, get revaccinated with the meningococcal vaccine. Ask your doctor if you are not sure if you need to be revaccinated.

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 influenzae type b (Hib). Certain people may be at risk of serious infections with gonorrhea. Talk to your doctor about whether you are at risk for gonorrhea infection, about gonorrhea prevention, and regular testing. Certain fungal infections (aspergillus) may also happen if you take SOLIRIS and have a weak immune system or a low white blood cell count.

What is SOLIRIS?

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

- patients- with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH).
- adults and children with a disease called atypical Hemolytic Uremic Syndrome (aHUS). SOLIRIS is not for use in treating people with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- adults with a disease called generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive
- adults with a disease called neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

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

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.
- receive 2 weeks of antibiotics if you immediately start SOLIRIS.
- stay up-to-date with all recommended vaccinations during treatment with SOLIRIS.

Know the medications you take and the vaccines you receive. 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 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
  - kidney problems
  - drop in your platelet counts
  - blood clots
  - confusion
  - difficulty breathing
  - chest pain
- **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
  - difficulty breathing
  - confusion
  - kidney problems
  - seizure
  - swelling in arms or legs
  - chest pain (angina)
  - 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
- diarrhea
- high blood pressure (hypertension)
- common cold (upper respiratory infection
- stomach-area (abdominal pain)
- vomiting
- pain or swelling of your nose or throat (nasopharyngitis)
- low red blood cell count (anemia)
- cough
- swelling of legs or feet (peripheral edema
- nausea
- urinary tract infections
- fever

The most common side effects in people with gMG treated with SOLIRIS include:

- muscle and joint (musculoskeletal) pain

The most common side effects in people with NMOSD treated with SOLIRIS include:

- common cold (upper respiratory infection)
- pain or swelling of your nose or throat (nasopharyngitis)
- diarrhea
- back pain
- joint pain (arthralgia)
- throat irritation (pharyngitis)
- bruising (contusion)

- dizziness
- flu like symptoms (influenza) including fever, headache, tiredness, cough, sore throat, and body aches

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

Manufactured by Alexion Pharmaceuticals, Inc., 121 Seaport Boulevard, Boston, MA 02210 USA. US License Number 1743

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 06/2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166s431

REMS

Risk Evaluation and Mitigation Strategy (REMS) Document

Soliris (eculizumab) REMS Program

I. Administrative Information

Application Number:	BLA 125166
Application Holder:	Alexion Pharmaceuticals Inc.
Initial REMS Approval:	06/2010
Most Recent REMS Update:	06/2019

II. REMS 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

III. REMS Requirements

Alexion Pharmaceuticals, Inc. must ensure that healthcare providers, patients, and wholesaler-distributors comply with the following requirements:

1. Healthcare Providers who prescriber Soliris must:

To become certified to prescribe	1. Review the drug's Prescribing Information. 2. Review the following: Patient Safety Card, Prescriber Safety Brochure, and Patient Safety Brochure. 3. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program.
Before treatment initiation at least 2	4. Assess the patient's meningococcal

weeks prior to first dose	vaccine status and immunize patients. 5. Provide the patient with a prescription for a two-week course of antibiotic prophylaxis if Soliris must be started less than 2 weeks after the patient was immunized. 6. Counsel the patient using the Patient Safety Card, and Patient Safety Brochure. Provide a copy of the materials to the patient.
During treatment	7. Assess the patient for early signs of meningococcal infection and evaluate immediately, if infection is suspected. 8. Discontinue Soliris in patients who are being treated for serious meningococcal infections. 9. Revaccinate patients according to the Advisory Committee on Immunization Practices recommendations.
At all times	10. Report cases of meningococcal infection, including the patient's clinical outcomes to Alexion Pharmaceuticals, Inc.

2. Patients who are prescribed Soliris:

Before treatment initiation, at least 2 weeks prior to the first dose	1. Get meningococcal vaccines as directed by your doctor. 2. Take antibiotics as directed by your doctor for two weeks after you get your vaccine if you have to start Soliris right away. 3. Receive counseling from the prescriber using the Patient Safety Card and Patient Safety Brochure.

During Treatment	4. Get meningococcal vaccines as directed by your doctor.
At all times	5. Inform the prescriber or get emergency medical care right away if you experience 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. 6. Have the Patient Safety Card with you.

Alexion Pharmaceuticals, Inc. must provide training to healthcare providers who prescribe Soliris.

The training includes the following educational material(s): Prescriber Enrollment Form, Prescriber Safety Brochure, Patient Safety Brochure, and Patient Safety Card. The training must be available online or in hardcopy format via mail.

To support REMS Program operations, Alexion Pharmaceuticals, Inc. must:

1. Establish and maintain a REMS Program website, www.solirisrems.com. The REMS program website must include the capability to complete the prescriber certification or enrollment online, and the option to print the PI and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS program website. The REMS program website must not link back to the promotional product website(s).
2. Make the REMS Program website fully operational and all REMS materials available through the website and call center by 30 calendar days of REMS modification (06/28/2019).
3. Establish and maintain a REMS Program call center for REMS participants at 1-888-765-4747.
4. Establish and maintain a validated, secure database of all REMS participants who are certified in the Soliris REMS Program.
5. Ensure prescribers are able to enroll by fax, mail, email, and online.
6. Provide the Patient Safety Brochure, Patient Safety Card, and Prescriber Safety Brochure to prescribers annually.
7. Provide Prescriber Enrollment Form, Prescriber Safety Brochure, Patient Safety Brochure, and Patient Safety Card, and the Prescribing Information to health care providers who (1) attempt to prescribe and are not yet certified or (2) inquire about how to become certified.

To ensure REMS participants' compliance with the REMS Program, Alexion Pharmaceuticals, Inc. must:

8. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: Soliris distribution and dispensing and certification of prescribers. These records must be readily available for FDA inspections.
9. Establish a plan for addressing noncompliance with REMS Program requirements.
10. Monitor prescribers on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified including de-certification.

IV. REMS Assessment Timetable

Alexion Pharmaceuticals, Inc. must submit REMS assessments 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 calendar days before the submission date for that assessment. Alexion Pharmaceuticals, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the Soliris REMS:

Enrollment Forms:

Prescriber:

1. Prescriber Enrollment Form

Training and Educational Materials

Prescriber:

2. Prescriber Safety Brochure

Patient:

3. Patient Safety Card
4. Patient Safety Brochure

Other Materials

5. Soliris REMS Program Website

Prescriber Enrollment Form

SOLIRIS® (eculizumab) Injection for Intravenous Use | SOLIRIS REMS Program

Soliris is only available through a restricted program called the SOLIRIS REMS (Risk Evaluation and Mitigation Strategy). All prescribers must be specially certified. To become certified, prescribers must:

1) **Review** the SOLIRIS Prescribing Information, Prescriber Safety Brochure, Patient Safety Brochure and the Patient Safety Card.
2) **Enroll** in the SOLIRIS REMS by completing this form.
3) **Counsel** patients and provide them with the Patient Safety Brochure and Patient Safety Card.

There are 2 pages to this form. Complete page 1. Read the agreements and sign page 2.
Return BOTH pages to Soliris REMS.

You may complete this form
- online at www.solirisrems.com
- by fax at 1-877-580-2596 (ALXN)
- by scanning and emailing to REMS@alexion.com
- by mailing to Alexion Pharmaceutical, Inc. ATTN: REMS Program, 121 Seaport Boulevard, Boston, MA 02210

Prescriber Information: (please print)

First Name: _____ **MI:** ____ **Last Name:** _____

Prescriber NPI #: _____

Office Address: _____

City: _____ **State:** _____ **ZIP:** _____

Phone number: _____ **Fax:** _____

Email: _____

Continue to page 2 to read the agreement and sign the form. You must return BOTH sides of this form.

By completing, signing and submitting this form, I acknowledge and agree that:

- I have read and understand the SOLIRIS Prescribing Information (PI), *Prescriber Safety Brochure*, *Patient Safety Brochure,* and the *Patient Safety Card*.
- I understand the:
  - risk of meningococcal infections associated with SOLIRIS.
  - early signs of meningococcal infections
  - need for immediate medical evaluation of signs and symptoms with possible meningococcal infections
- Before treatment initiation at least 2 weeks prior to the first dose, I will:
  - Assess the patient's meningococcal vaccine status and immunize patients unless the risks of delaying Soliris therapy outweigh the risks of developing meningococcal infection.
  - Provide the patient with a prescription for a two-week course of antibiotic prophylaxis if Soliris must be started right away.
  - Counsel the patient about the signs and symptoms of meningococcal infections using the *Patient Safety Card*, and *Patient Safety Brochure*. Provide a copy of these materials to the patient. Instruct the patient to carry the *Patient Safety Card* at all times.
- During treatment, I will:
  - Assess the patient for early signs of meningococcal infection and evaluate immediately if infection is suspected.
  - Discontinue SOLIRIS in patients who are being treated for serious meningococcal infections.
  - Revaccinate patients according to the Advisory Committee on Immunization Practices recommendations.
- I will report cases of meningococcal infection including the patient's clinical outcomes to Alexion Pharmaceuticals, Inc.
- I understand that if I do not maintain compliance with the requirements of the SOLIRIS REMS, I will no longer be able to prescribe SOLIRIS.
- I understand that SOLIRIS REMS and its agents or contractors may contact me to support the administration of the SOLIRIS REMS.

Prescriber Signature **Date**

Print Name

Adverse Event Experiences

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.

This guide does not provide all risk information for Soliris.

Please see full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infection for more detailed safety information.

Reference ID: 4454988

ALEXION

Soliris REMS

Prescriber Safety Brochure

This brochure provides information on:

- The risk of meningococcal infection
- Patient meningococcal vaccination recommendations
- Monitoring Patients
- Counseling and providing your patients with a Patient Safety Brochure and Patient Safety Card

SOLIRIS® (eculizumab) Injection for Intravenous Use

Risk of 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.
- Soliris is associated with an approximate 2,000-fold increased risk of meningococcal disease in comparison to the general U.S. population annual rate (0.14 per 100,000 population in 2015).

Immunization

- **Immunize all 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.
- **Provide 2 weeks of antibacterial drug prophylaxis to patients if Soliris must be initiated immediately and vaccines are administered less than two weeks before starting 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.
- If urgent Soliris therapy is indicated in an unvaccinated patient, administer meningococcal vaccines(s) as soon as possible.
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections.**
- Comply with the most current Advisory Committee on Immunization Practices (AC P) recommendations for meningococcal vaccination in patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendation, considering the duration of Soliris therapy.

Monitoring Patients

- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.
- Discontinue Soliris in patients who are being treated for serious meningococcal infections

Patient Counseling

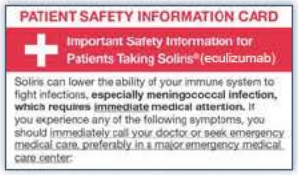
Counsel and provide your patients with both the **Patient Safety Brochure** and **Patient Safety Card.**

- Tell your patients about the risk of meningococcal infections and that this risk may continue for several weeks after the last dose of Soliris.
- Instruct your patients to seek immediate medical attention if they develop any of the following symptoms:
  - Headache with nausea or vomiting
  - Headache with a stiff neck or stiff back
  - Fever and rash
  - Muscle aches with flu-like symptoms
  - Headache and a fever
  - Fever
  - Confusion
  - Eyes sensitive to light


What You Need to Know About Soliris

Patient Safety Card

The card has important safety guidance for both patients and any healthcare provider that may see or treat your patient for medical care.


PATIENT SAFETY INFORMATION CARD

Important Safety Information for Patients Taking Soliris® (eculizumab)

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:

- Discuss the importance and the proper use of this safety card with every patient.
- **Tell your patients to carry this card at all times.**
- Instruct patients to show the card to any healthcare professional involved in their care.

Soliris REMS (Risk Evaluation and Mitigation Strategy)

A REMS is a program required by the FDA to manage known or potential serious risk associated with a drug program. Soliris is available only through a restricted program under a REMS. Healthcare providers who prescribe Soliris must be specially certified. Certification consists of review of REMS education materials and enrollment in the Soliris REMS program.

Visit www.solirisREMS.com or call 1-888-SOLIRIS (765-4747) to learn more about the Soliris REMS. Enrollment can also be completed online at www solirisrems com

Indication 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).

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

Soliris is indicated for the treatment of Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

Reference ID: 4454988

PATIENT SAFETY CARD

Important Safety Information for Patients Taking Soliris® (eculizumab)

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.

Keep this card with you at all times, even if you stop using Soliris. Your risk of meningococcal infection may continue for several weeks after your last dose of Soliris.

Reference ID: 4454988

PATIENT SAFETY CARD

Information for the Treating Physician

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

- Meningococcal infections may become 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. In case of safety concerns, 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)

Soliris® is a registered trademark of Alexion Pharmaceuticals, Inc.

Reference ID: 4454099

What You Need to Know About Soliris

What is Soliris?

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

What are the serious risks of Soliris?

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.

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**

Getting Your Vaccine

- Meningococcal vaccines lower the risk of getting a meningococcal infection. However, this vaccine will not prevent all meningococcal infections.
- You must receive a meningococcal vaccination at least 2 weeks before your first dose of Soliris unless you have already had this vaccine(s).
- If your doctor decides that urgent treatment with Soliris is needed, you should receive the meningococcal vaccination as soon as possible.
- If you have not been vaccinated and you must take Soliris right away, you should also receive 2 weeks of antibiotics with your vaccinations
- If you had a meningococcal vaccine in the past, you might need additional vaccination before you start Soliris. Your doctor will decide if you need additional meningococcal vaccination.

Patient Safety Card

You will receive a Patient Safety Card from your health care provider.

- Carry thus card at all times.
- **Show this card to any healthcare professional who treats you. This will help them diagnose and treat you quickly.**
- Get treatment right away for any symptoms of a meningococcal infection even if you do not have your card on you.

PATIENT SAFETY INFORMATION CARD

Important Safety Information for Patients Taking Soliris® (eculizumab)

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:

Reference ID: 4454988

SOLIRIS®
(eculizumab)
Injection for Intravenous Use

SOLIRIS REMS (Risk Evaluation and Mitigation Strategy)

What is the Soliris REMS?

A REMS (**R**isk **E**valuation and **M**itigation **S**trategy) is a program required by the Food and Drug Administration (FDA) to manage known or potential serious risks associated with a drug product.

The purpose of the SOLIRIS REMS is to mitigate the occurrence and morbidity associated with meningococcal infections by informing healthcare providers and patients about the:

- Increased risk of meningococcal infections with Soliris
- Early signs of invasive meningococcal infections, and
- Need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections.

Download the Patient Safety Card

Download Patient Safety Brochure

Soliris REMS

Contact us
Phone:
1.888.SOLIRIS (1.888.765.4747)
FAX: 1.877.580.2596 (ALXN)

Hours of Operation:
Monday – Friday
8:30 am – 5:00 pm
Eastern Time

Program Requirements

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).
HCPs who prescribe Soliris must be specifically certified. Certification consists of review of REMS educational materials and enrollment in the SOLIRIS REMS.

Healthcare Provider Certification

Certification in the SOLIRIS REMS includes the following steps:

1

Review the SOLIRIS REMS HCP Educational Materials:

- Prescribing Information
- Prescriber Safety Brochure
- Patient Safety Brochure
- Soliris Patient Safety Card

Enroll in the SOLIRIS REMS Program:

Click here to complete the SOLIRIS REMS Prescriber Enrollment online

OR

Print and sign the Prescriber Enrollment Form

- Mail the form to Soliris REMS, Alexion Pharmaceuticals, 121 Seaport Boulevard, Boston, MA 02210.
- Fax the form to Soliris REMS at 1-877-580-2596 (ALXN); or
- Scan and email the form to rems@alexion.com

2

Patient Counselling

HCPs should

- Counsel patients using both the Patient Safety Brochure and Patient Safety Card. Provide these materials to your patients.
- Remind patients to carry the Patient Safety Card with them at all times.
- Advise their patients that this safety card contains important safety information about the risk of meningococcal infection that they need to be aware of before they are given Soliris and during their treatment with Soliris.
- Remind their patients to show this card to any doctor involved in their treatment.
- Explain to their patients that if they cannot reach their doctor, they should go to the emergency room immediately and show the emergency room staff the Soliris Patient Safety Card. Even if a patient stops using Soliris, they should keep their Soliris Patient Safety Card with them.

To order a Soliris Patient Safety Card, contact Soliris REMS at 1.888.SOLIRIS (1.888.765.4747).
The Spanish versions of the Patient education material can be downloaded from below:

- Spanish Soliris Patient Safety Card
- Spanish Patient Safety Brochure

Reporting Adverse Events

HCPs should report all suspected adverse events, including reports of meningococcal infection by contacting Alexion Pharmaceuticals, Inc. at 1.888.Soliris (1.888.765.4747); 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 http://www.fda.gov/MedWatch

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166s431

CROSS DISCIPLINE TEAM LEADER REVIEW

Summary Memorandum for Regulatory Action

Date	June 27, 2019
From	Paul Lee, MD, PhD Nick Kozauer, MD Billy Dunn, MD
Subject	Summary Memorandum for Regulatory Action
BLA # and Supplement#	125166 (422)
Applicant	Alexion Pharmaceuticals, Inc.
Date of Submission	December 28, 2018
PDUFA Goal Date	June 28, 2019
Proprietary Name	Soliris
Established or Proper Name	Eculizumab
Dosage Form(s)	Solution for intravenous injection
Applicant Proposed Indication(s)/Population(s)	The treatment of (b) (4) Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive
Applicant Proposed Dosing Regimen(s)	900 mg weekly for 4 weeks, followed by 1200 mg for the fifth dose 1 week later, and then 1200 mg every 2 weeks thereafter
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 antibody positive
Recommended Dosing Regimen(s) (if applicable)	900 mg weekly for 4 weeks, followed by 1200 mg for the fifth dose 1 week later, and then 1200 mg every 2 weeks thereafter

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Neuromyelitis optica spectrum disorder (NMOSD), formerly known as NMO or Devic's Disease, is an autoimmune disease that is characterized by clinical relapses, or "attacks," in which patients experience inflammation of the optic nerve (optic neuritis), spinal cord (transverse myelitis), or brainstem. These inflammatory episodes can cause blindness, paralysis, loss of sensation, bowel or bladder dysfunction, and other serious, disabling symptoms. Almost all patients with NMOSD have more than one relapse. Few patients who experience an NMOSD attack have a full recovery. More than half of patients with NMOSD have permanent blindness or paralysis as the result of NMOSD attacks. If inflammation compromises regions involved in breathing or heart function, NMOSD relapses can be fatal.

The average age of onset of NMOSD is approximately forty years, though onset can occur throughout the lifespan. The ratio of men to women with NMOSD is greater than 2:1. The epidemiology of NMOSD is complex and differs greatly depending on the region and the ethnicity of the study population. The incidence of NMOSD is estimated between 0.05-0.4 per 100,000 population, and the prevalence estimates vary from 0.5-10 per 100,000 population. African and Danish subpopulations appear to be at highest risk of developing NMOSD. Though rare, NMOSD cases can cluster in families who have human leukocyte antigen genotypes conferring a genetic susceptibility to autoimmunity.

The pathophysiology of NMOSD is not fully understood, but many patients with NMOSD have antibodies directed against the aquaporin-4 (AQP4) protein which form membrane bound water transporters in cells throughout the central nervous system (CNS). AQP4 is highly expressed in the optic nerves, spinal cord, and area postrema of the brainstem, and it is these regions of the CNS that are often targeted for inflammation in NMOSD relapses. However, there are patients who do not have antibodies directed against AQP4 who experience NMOSD attacks. Therefore, the current NMOSD diagnostic criteria in widespread use rely on the presence of cardinal clinical features such as optic neuritis and longitudinally extensive transverse myelitis. A positive assay for anti-AQP4 antibodies is not required for definitive diagnosis of NMOSD. Patients who test negative for anti-AQP4 antibodies may have antibodies directed against other CNS proteins, different lesion distributions, and monophasic clinical courses.

Soliris (eculizumab) is a recombinant humanized monoclonal IgG2/4κ antibody that binds specifically to complement component 5 (C5). Eculizumab inhibits the cleavage of C5 into its active forms, C5a and C5b. By inhibiting activation of C5, eculizumab prevents the formation of the terminal complement complex and interrupts the final step of the alternate pathway in the complement cascade which would lead to complement-mediated tissue destruction. Terminal complement activation is believed to play a prominent role in anti-AQP4 antibody related inflammation in NMOSD.

Soliris (eculizumab) is already approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic anemia uremic syndrome (aHUS), and refractory generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor antibody positive. Eculizumab was granted Orphan Drug Designation in 2013 for the treatment of NMOSD.

The applicant has provided data from Study ECU-NMO-301 (Study 301 in this memorandum), a prospective, randomized, placebo-controlled trial of the effect of eculizumab treatment on the time to the first on-treatment relapse compared to treatment with placebo in 132 patients diagnosed with NMOSD who had anti-AQP4 antibodies. This trial evaluated a 900 mg dose of eculizumab given intravenously weekly for 4 weeks, followed by 1200 mg for the fifth dose 1 week later, and then 1200 mg every 2 weeks thereafter compared to placebo. The study protocol allowed patients to remain on some unapproved standard-of-care immunosuppressant therapies, and there were enrolled patients who were receiving no concurrent immunosuppressant therapies. The primary efficacy outcome measure of the trial was the time to first relapse. The key secondary outcome efficacy measures were the annualized relapse rate, the change in the Expanded Disability Status Scale (EDSS) score from baseline to end of study (EOS), the change in the modified Rankin Score from baseline to EOS, the change in the Hauser Ambulation Index from baseline to EOS, and the change in the European Quality of Life-5 Dimension Questionnaire from baseline to EOS.

In Study 301, patients in the eculizumab treatment arm had a highly statistically significant ($p<0.0001$) 94% reduction in relative risk of an NMOSD relapse than patients in the placebo treatment arm. Patients treated with eculizumab had a highly statistically significant ($p<0.0001$) 96% reduction in relative annualized relapse rate, experiencing an average rate of 0.066 relapses per year as compared to 0.446 relapses per year in placebo-treated patients. The change in EDSS score from baseline to EOS was not significantly different between the two treatment arms. The subsequent key secondary efficacy outcome measures, described nominally because of the lack of significance in the EDSS, showed trends towards improvements though the trial's time-to-event design raises questions about the interpretability of these observations.

Given the clear, robust efficacy findings of eculizumab for the treatment of NMOSD, a serious, disabling disease with no FDA-approved therapies, reliance on a single clinical trial is justified. Study 301 only enrolled patients who had antibodies to AQP4. (b) (4) [redacted] The safety findings in the trial population with NMOSD with anti-AQP4 antibodies did not identify new risks of eculizumab not already known from eculizumab's use in several other indicated populations. The most severe risk associated with eculizumab treatment, increased susceptibility to meningococcal infections, is described in a boxed warning in the labeling of eculizumab and is the subject of a risk evaluation and mitigation strategy (REMS) that will be modified to include the NMOSD indication. None of the patients with NMOSD treated with eculizumab experienced meningococcal infections. The existing labeling warnings and precautions and REMS program are adequate to ensure continued safe use of eculizumab.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• NMOSD is an autoimmune condition that is associated with recurrent attacks that predominantly involve the spinal cord and optic nerves. • NMOSD attacks can result in severe and largely irreversible neurologic disability, including blindness, paralysis, and death due to respiratory failure. • The spectrum of the severity of attacks in patients with NMOSD is uncertain. Although some attacks may be very severe, others may result in mild or moderate disability. Full recovery from NMOSD attacks is rare. • Current international consensus diagnostic criteria define NMOSD based on the presence of core features of NMOSD such as optic neuritis, acute myelitis, and brainstem lesions causing severe nausea, vomiting, or hiccups. Unlike prior diagnostic criteria, a positive anti-aquaporin-4 (AQP4) IgG test is not necessary for a diagnosis of NMOSD. Instead, current criteria add an additional qualifier for serological status describing whether a patient has a positive or negative anti-AQP4 serum antibody test. • The global prevalence of NMOSD is between 0.5 and 10 per 100,000 population. There may be as many as 12,000 patients with NMOSD in the United States. Danish and Caribbean-Africans appear to be at highest risk of being diagnosed with NMOSD.	NMOSD is a serious, disabling, and potentially fatal disease. Most patients with NMOSD have anti-AQP4 antibodies. It is unclear if there are similarities in response to treatment and clinical outcomes in patients with NMOSD who have anti-AQP4 antibodies and patients with NMOSD who lack these antibodies.
Current Treatment Options	• There are no approved treatments for NMOSD • Unapproved immunosuppressant therapies currently used to treat NMOSD have not been studied in adequate and well-controlled studies.	There is an unmet medical need for an effective treatment for NMOSD. Immunosuppression therapies used currently do not have established efficacy in the condition.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The applicant provides data from a 2:1 randomized, double-blind, placebo-controlled time to event trial in 132 adult patients with NMOSD treated with eculizumab or placebo in which the primary outcome efficacy measure was the time to first relapse on trial. • Eculizumab treatment reduced the relative risk of a relapse by 94% relative to standard or care or no concurrent immunosuppressant treatment. • Eculizumab treatment reduced the annualized relapse rate by 96% compared to placebo superimposed on standard of care or no concurrent immunosuppressant treatment.	The data from the clinical trial provided in this application establish the effectiveness of eculizumab for the treatment of NMOSD in adult patients who are anti-AQP4 antibody positive. Relapses are significant clinical events that can cause permanent disability. Preventing and reducing the frequency of relapses is a meaningful clinical outcome for patients with NMOSD.
Risk and Risk Management	• The key risk of treatment with eculizumab is the risk of increased susceptibility to infections due to interference with the complement pathway. Patients treated with eculizumab appeared to have a 1% higher risk of serious infections (most commonly, pneumonia) than placebo-treated patients. This risk may be higher for infections with encapsulated organisms, most notably *Neisseria meningitidis*. • There was one death in Study 301 from respiratory failure secondary to pneumonia. The patient had a history of cardiac disease and recurrent pneumonia due to chronic lung disease that predated enrollment in this trial. Eculizumab did not appear to be the primary cause of death. • The NMOSD development program for eculizumab did not reveal any previously unidentified risks associated with eculizumab treatment for its approved indications (i.e., atypical hemolytic uremic syndrome, paroxysmal nocturnal hemoglobinuria, and generalized myasthenia gravis in adult patients with anti-MuSK	The safety data from the current development program support approval and are consistent with the product's established safety profile for its approved indications. All patients received immunization against meningococcal meningitis. There were no cases of meningococcal meningitis in the trial. It is uncertain if the trial represents the true incidence of these types of infection in patients with NMOSD being treated with eculizumab because of the short duration of the trial and the small number of subjects studied. There is a Risk Evaluation and Mitigation Strategy (REMS) in place for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	antibodies).	eculizumab that requires *Neisseria meningitidis* vaccination before treatment and seeks to reduce risk of infection and ensure prompt treatment if infection occurs. The current labeling for eculizumab provides adequate information to inform prescribers and patients regarding the risks of treatment in the NMOSD population.

2. Background

This efficacy supplement to the BLA contains data in support of the efficacy of eculizumab, administered as an intravenous (IV) injection, for the treatment of (b) (4) neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody positive. Eculizumab was approved under the trade name Soliris for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in 2007. Eculizumab received accelerated approval for the treatment of atypical hemolytic anemia uremic syndrome (aHUS) in 2011, with a conversion to a full approval in 2014. In 2017, eculizumab was approved for the treatment of patients with refractory generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor antibody positive.

NMOSD is a chronic disabling disease that is characterized by acute exacerbations, or relapses, in which patients experience inflammatory lesions within the central nervous system, most typically manifesting as optic neuritis or transverse myelitis. Relapses, also sometimes referred to as "attacks," can occur in one or both optic nerves, the spinal cord, the brainstem, and, less commonly, the brain. These relapses can result in blindness, weakness, paraplegia, loss of sensation, stroke-like symptoms, and bowel/bladder/sexual dysfunction. In rare instances when a lesion compromises central respiratory function or other critical functions, NMOSD relapses can be fatal.

Most patients with NMOSD are young women, though NMOSD can be diagnosed at any age. Estimates vary, but the number of patients in the United States meeting diagnostic criteria for NMOSD may range between 4,000 and 12,000. Worldwide, there is considerable variability in the prevalence of NMOSD with broad differences observed based on geography and ethnicity. The prognosis for patients with NMOSD is typically poor; most patients accumulate significant disability due to the cumulative effects of relapses. Estimates of mortality due to NMOSD-related sequelae range from 7-32%.

NMOSD is an autoimmune inflammatory disease and appears to result from the production of antibodies that, in most cases, recognize AQP4. In the spinal cord and optic nerve, AQP4 is one of the primary channels that permit water transit through the cell membrane; AQP4 is particularly concentrated on the end feet processes of astrocytes. The creation of anti-AQP4 antibodies appears to be a pathognomonic step in the acquisition of NMOSD, and over half of patients diagnosed with NMOSD will have a detectable titer of anti-AQP4 antibodies in their serum or spinal fluid.

Eculizumab is a recombinant monoclonal antibody that binds to the complement protein C5, and, in turn, inhibits the cleavage of C5 into C5a and C5b, which prevents formation of the terminal complement complex C5b-9 (also termed the "membrane attack complex" or MAC). Terminal complement activation is strongly associated with anti-AQP4 antibodies and appears to be one of the final common pathways leading to glial and axonal injury in NMOSD relapses.

There are no FDA-approved treatments for NMOSD. The standard of care with the goal of preventing relapses due to NMOSD is chronic immunosuppression with therapies that reduce the number of lymphocytes, such as corticosteroids, azathioprine, or rituximab. High-dose corticosteroids and plasma exchange are used when patients experience acute relapses. None of the therapies commonly used to treat NMOSD on an acute or chronic basis have been shown to be effective in preventing/delaying relapses, nor have they demonstrated a significant effect on disability outcomes. Two-thirds of patients with NMOSD on standard of care chronic immunosuppressants are reported to continue to experience relapses. An estimated 60% of patients with NMOSD have permanent blindness or paraplegia due to the sequelae of relapses. There is a significant unmet medical need in NMOSD for an effective therapy that prevents acute relapses and to delay or prevent disability from acute attacks.

This application contains data from Study ECU-NMO-301 (henceforth "Study 301"), a prospective, randomized, placebo-controlled trial as the primary basis of support for the effectiveness of eculizumab in the treatment of NMOSD. Additional supportive information comes from the open-label extension phase of Study 301, ECU-NMO-302 (henceforth, "Study 302").

Dr. Lawrence Rodichok's clinical review provides the regulatory history of the development program for eculizumab for the treatment of NMOSD. This development program was granted Orphan Drug Designation for the treatment of NMOSD in June 2013.

3. Product Quality

Not applicable. Eculizumab is an approved product. There are no product quality issues unique to this application. Therefore, there was no Product Quality team review.

4. Nonclinical Pharmacology/Toxicology

Not applicable. Eculizumab is an approved therapy. Nonclinical studies were not necessary to support this efficacy supplement application.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) provided an integrated review. Dr. Hristina Dimova wrote the primary review for OCP; the clinical pharmacology team leads were Drs. Angela Men and Kevin Krudys. Drs. Atul Bhattaram and Angela Men provided a labeling review.

The OCP review cites the pharmacokinetic (PK) and pharmacodynamic (PD) findings established in prior applications for the PNH, aHUS, and gMG indications and notes that the dosing regimen used in Study 301 is the same dosing regimen previously shown to achieve complete and sustained inhibition of terminal complement in the trials for these other approved indications. Study 301 contributed PK/PD data and anti-drug antibody (ADA) data derived from patients with NMOSD. The OCP review found the new studies were acceptable and confirmed that the PK/PD findings in NMOSD patients were very similar to findings in patients with PNH, aHUS, and gMG. The OCP review provides more data that ADAs are not commonly associated with eculizumab therapy. Only 2 out of 96 patients with NMOSD treated with eculizumab has detectable ADAs, and none of the eculizumab-exposed patients had neutralizing ADAs.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

This BLA supplement proposes changing the labeling for eculizumab to add an indication for the treatment of NMOSD in (b) (4) who are positive for the anti-AQP4 antibody. New efficacy evidence comes from a 132-person clinical trial, named Study ECU-NMO-301 (Study 301), in adults with NMOSD who tested positive for anti-AQP4 antibodies.

Dr. Lawrence Rodichok was the clinical reviewer for this application. Dr. Sharon Yan was the biometrics reviewer, Dr. Kun Jin was the biometrics team lead, and Dr. Hsien Ming (Jim) Hung was the biometrics Division Director for this application.

Dr. Rodichok states that Study 301 provides substantial evidence of efficacy in treating relapses in NMOSD and recommends approval.

Dr. Yan concludes that the efficacy results from Study 301 provide sufficient evidence that eculizumab is effective in reducing the relapse rate and in delaying relapses.

This review agrees with the conclusions of Drs. Rodichok and Yan.

Study 301

Study 301 was a 2:1 randomized, double-blind, placebo-controlled, multicenter, prospective study of the effect of eculizumab treatment, with or without the continuation of prior unapproved immunosuppressant treatment to prevent relapses, on the time to the first on-treatment relapse compared to treatment with placebo.

Inclusion criteria for Study 301 were a clinical definition of "neuromyelitis optica" (NMO) as defined by clinical criteria published by Wingerchuk in 2006 and revised in 2007. Enrolled patients also had tested positive for anti-AQP4 antibodies, had experienced at least two relapses in the year prior to screening (or three relapses within the two years before screening), and had an Expanded Disability Status Scale (EDSS) score of 7 or less. Since this study's initial design, there have been revisions to the international criteria used to diagnose NMO, which is now termed NMOSD. Dr. Rodichok indicates that the patients' clinical presentations and AQP4 positive antibody status at baseline means that they would meet the current international consensus criteria for a diagnosis of "NMOSD with AQP4 antibodies." Therefore, the study's use of the older, now superseded, criteria to define patients' diagnoses does not create a conflict with assigning an indication for the treatment of "NMOSD in adult patients with AQP4 antibodies," which would be the appropriate current nomenclature to describe the enrolled patient population.

The study plan anticipated randomizing up to 132 patients at up to 150 centers. The sample size of 132 patients was based on the assumption of a 40% relapse-free rate in the placebo group and a hazard ratio of 0.24 using the log-rank test for the comparison of eculizumab to placebo for the primary analysis. That would yield a power of 90%. The final plan was to observe 24 relapses in 24 patients. The applicant terminated the study prematurely at 23 adjudicated relapses because there had been no relapses in the prior two years, and the applicant deemed it unnecessary to await the 24th relapse.

Eligible patients were randomized on Day 1 to treatment with either eculizumab or placebo in a 2:1 ratio. Randomization was stratified by EDSS score at randomization ($\leq$ 2.0 and $\geq$2.5 to <7.0) and by immunosuppressant therapy (IST) status (treatment naïve, continuing on the same IST since last relapse, or changed/added IST since last relapse). The protocol of Study 301 allowed enrolled patients to continue treatment with specified ISTs provided that the dose of the ISTs had been stable prior to randomization and remained stable throughout the blinded treatment period. Patients were to remain on their assigned treatment until a protocol-defined relapse occurred or until the trial was terminated at the pre-determined number of distinct adjudicated relapses. Patients who completed the trial to a relapse or trial termination were eligible to enter an extension study of open-label eculizumab treatment (OLE).

Dr. Rodichok notes that the Division granted a Special Protocol Assessment (SPA) agreement to the Study 301 protocol in May 2013. This SPA agreement was rescinded in November 2013, when the applicant revealed that it anticipated enrolling no "treatment naïve"

(defined as "those who have received or are receiving either no IST or have received only corticosteroids following treatment of acute relapses prior to the screening") patients as it had previously agreed to do. Without this cohort of treatment naïve patients, the Division was concerned that the interpretation of the study's outcome analyses would be difficult because of the study's allowance for potentially all patients to continue concomitant treatment with unapproved ISTs. The Division felt that this treatment naïve group, a population not being treating with another IST that could provide a potential contribution to efficacy, was important to establish a treatment effect solely attributable to eculizumab. Dr. Rodichok notes that the applicant underestimated the enrollment of patients not taking an IST. Approximately 25% of the eculizumab and the placebo treatment arms in Study 301 met the protocol definition for treatment naïve.

The primary objective of Study 301 was to assess the efficacy and safety of eculizumab, as compared with placebo, in patients who meet the current clinical definition of NMOSD. The primary outcome event measure was time to first relapse.

The protocol defined a "relapse" as any new onset or worsening of previous neurologic symptoms with an objective change on neurologic examination that persisted for 24 hours or more, was attributable to NMOSD, and was not due to an alternate identifiable cause such as an infection, excessive exercise, or high ambient temperature. The treating physician made the determination of whether the event met the protocol definition of a relapse. The treating physician determined the appropriate acute treatment for the relapse, including whether to change any concurrent IST. The severity of the relapse was determined using the assessments as conducted by the treating physician. Dr. Rodichok's review notes that an amendment to the study protocol implemented in July 2016, established a relapse adjudication process in which a Relapse Adjudication Committee (RAC), composed of three neurologists or neuro-ophthalmologists external to the applicant and blinded to treatment assignment, would review all investigator-reported relapse events and a decision regarding whether a relapse would be deemed an on-trial protocol-defined relapse would be rendered by the RAC in a majority vote. In Amendment 9 of the Study 301 protocol, the applicant explained that the rationale for creating the RAC was to address an evident need for a more standardized approach to defining relapses due to "variability observed across sites in the diagnosis of relapse events." Dr. Rodichok notes that this committee was convened after 93 patients had been randomized and 23 relapses had occurred. He expressed concern that the RAC adjudicated confirmation rates of the previously investigator-determined relapses differed between events in the eculizumab and placebo treatment groups and suggested a possible bias. Ultimately, the treating investigators in Study 301 reported 43 distinct relapse events in placebo-treated patients and 36 unique relapse events in eculizumab patients. However, in the eculizumab-treated patients, the RAC confirmed just 8% (3/36) of investigator-reported relapses as protocol-defined relapses whereas the RAC confirmation rate for placebo treatment patients was 49% (21/43). Dr. Rodichok requested the materials used by the RAC to adjudicate relapses; he notes in his review that the 3 confirmed events (2 optic neuritis attacks and 1 myelitis attack) in eculizumab-treated patients were appropriately adjudicated as relapses whereas the other 33 events were nonspecific neurological symptoms or transient phenomena that did not meet the protocol definition of a relapse. His review also notes that the 21 adjudicated relapses in the placebo group met the protocol definition of a relapse, tended to be more extensive,

and were associated with greater symptom severity than the 3 relapses in the eculizumab group. Therefore, Dr. Rodichok concludes that the RAC-adjudicated relapses are appropriate to serve as the basis of the primary efficacy analysis.

The following table, copied from Dr. Yan's review, presents the results of the primary efficacy analysis:

Table 1: Analysis of Time to First Adjudicated On-Trial Relapse

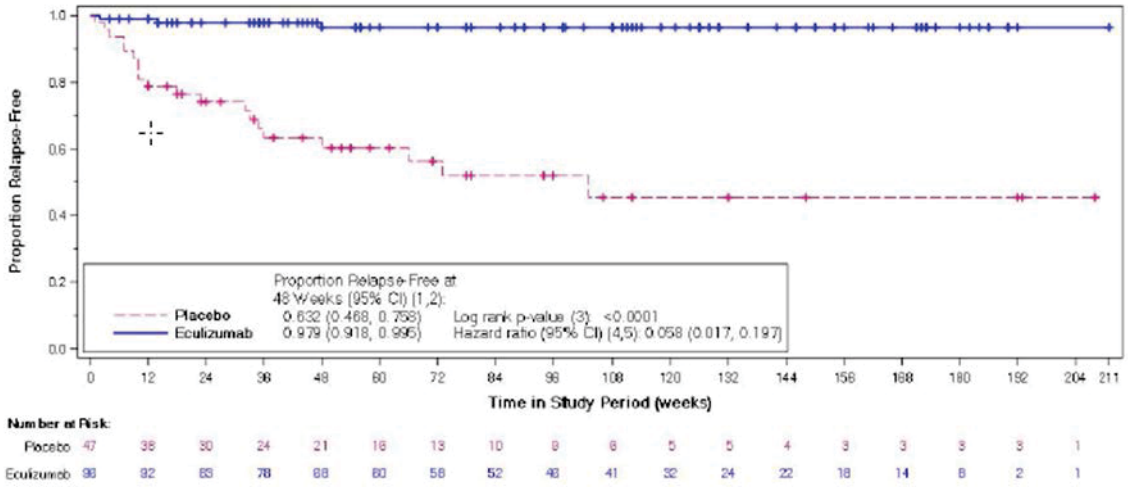
Variable	**Statistic**	**Placebo N=47**	**Eculizumab N=96**
Patients with Adjudicated Relapse	n (%)	20 (42.6)	3 (3.1)
Time to 1st Adjudicated Relapse			
Treatment effect – log-rank test	p-value		< 0.0001
Secondary test – Cox model	Hazard ratio (HR)		0.058
	95 C.I. of HR		(0.017, 0.197)
	% of reduction		94.2
	p-value		<0.0001
Sensitivity Analysis			
Time to first On-trial Relapse			
Patient with on-trial relapse	n (%)	29 (61.7)	14 (14.6)
Log-rank test	p-value		< 0.0001
Cox model	p-value		<0.0001
	Hazard ratio (HR)		0.180
	95 C.I. of HR		(0.095, 0.343)
	% of reduction		82.0

Source: Biometrics Reviewer's analysis

As the table indicates, the primary efficacy analysis of Study 301 achieved statistical significance ($p<0.0001$). Sensitivity analyses of the primary endpoint, including a sensitivity analysis of all investigator-identified relapses, confirmed the significant finding. Eculizumab treatment was associated with a 94.2% reduction in relative risk of relapse as compared to placebo treatment.

The following figure, copied from Dr. Yan's review, presents the Kaplan-Meier estimate to first adjudicated on-trial relapse:

Figure 1: Kaplan-Meier Estimated for Time to First Adjudicated On-Trial Relapse



Source: Biometrics Reviewer's analysis

This figure demonstrates a statistically significant sustained absence of relapses, beginning before 12 weeks of treatment, in the patients treated with eculizumab.

The key secondary outcome measures, in hierarchical order, were:

- Annualized relapse rate
- Change in EDSS at End of Study (EOS)
- Change in modified Rankin Score as EOS
- Change in Hauser Ambulation Index at EOS
- Change in European Quality of Life-5 Dimension Questionnaire at EOS

The following table, copied from Dr. Yan's review, presents the results of the annualized relapse rate analysis:

Table 2: Analysis of Annualized Relapse Rate

Variable	**Statistic**	**Placebo N=47**	**Eculizumab N=96**
Number of Adjudicated Relapses	Total	21	3
Patients with 0 adjudicated relapse	n (%)	27 (57.5)	93 (96.9)
Patients with 1 adjudicated relapse	n (%)	19 (40.4)	3 (3.1)
Patients with 2 adjudicated relapses	n (%)	1 (2.1)	0
Adjusted Adjudicated ARR	Rate	0.350	0.016
	95% CI	(0.199, 0.616)	(0.005, 0.050)
	Rate ratio		0.045
	95% CI of the ratio		(0.013, 0.151)
	p-value		<0.0001
Number of On-Trial Relapses	Total	31	14
Patients with 0 relapse	n (%)	18 (38.3)	82 (85.4)
Patients with 1 relapse	n (%)	27 (57.5)	14 (14.6)
Patients with 2 relapses	n (%)	2 (4.3)	0
Adjusted On-Trial ARR	Rate	0.446	0.066
	95% CI	(0.272, 0.732)	(0.036, 0.120)
	Rate ratio		0.147
	95% CI of the ratio		(0.078, 0.278)
	p-value		<0.0001

Source: Biometrics Reviewer's analysis

The table indicates that the secondary efficacy analysis of annualized relapse rate is significant ($p<0.0001$). Treatment with eculizumab was associated with a 95.5% reduction (0.446 to 0.066) in the annualized relapse rates of patients with NMOSD.

The following table, copied from Dr. Yan's review, presents the results of the analysis of change from baseline in EDSS at the EOS.

Table 3: Analysis Change from Baseline to EOS in the EDSS

Variable	Statistic	Placebo N=47	Eculizumab N=96
Baseline EDSS Score	Mean (SD) Median	4.26 (1.51) 4.0	4.15 (1.65) 4.0
Change in EDSS No change Increase (worsening) Decrease (improvement)	Mean (SD) Median n (%) n (%) n (%)	0.12 (0.95) 0 20 (42.6%) 13 (27.7%) 14 (29.8%)	-0.18 (0.81) 0 49 (51.0%) 19 (19.8%) 13 (13.5%)
Primary Analysis: Rank ANCOVA	p-value		0.4464
Applicant: Randomization Based Non-parametric ANCOVA	p-value		0.0597
Sensitivity Analysis ANCOVA on original score	LS mean (SE) p-value	0.03 (0.133)	-0.26 (0.096) 0.0603
Sensitivity Analysis MMRM	LS mean (SE) p-value	-0.30 (0.101)	-0.38 (0.070) 0.4855

Source: Biometrics Reviewer's analysis

Dr. Yan notes in her review that in the latest version of the Statistical Analysis Plan, the applicant changed the analysis for change in EDSS from a rank based ANCOVA to a non-parametric ANCOVA, but the applicant did not provide the necessary information to confirm the non-parametric ANCOVA, and thus her analysis confirms only the rank-based analysis findings as the primary analysis method. However, both ANCOVA methods yielded findings that were not statistically significant. Dr. Yan also notes that the median change in EDSS was 0 for both treatment groups, and that over 70% of eculizumab-treated patients had the same or experienced worsening of their EDSS scores at the EOS assessment.

The following table, copied from Dr. Yan's review, presents the results of the analysis of the change from baseline to EOS in the modified Rankin Score (mRS):

Table 4: Analysis of Change from Baseline to EOS in the mRS

Variable	Statistic	Placebo N=47	Eculizumab N=96
Baseline mRS Score	Mean (SD) Median	2.15 (0.98) 2.0	2.15 (1.14) 2.0
Change in mRS	Mean (SD) Median	0.09 (0.75) 0	-0.24 (0.72) 0
No change Increase (worsening) Decrease (improvement)	n (%) n (%) n (%)	35 (74.5%) 7 (14.9%) 5 (10.6%)	65 (67.7) 6 (6.3%) 25 (26.0%)
Primary Analysis: Rank ANCOVA	Nominal p-value		0.0135
Sensitivity Analysis ANCOVA on original score	LS mean (SE) Nominal p-value	0.00 (0.115)	-0.32 (0.084) 0.0154
Sensitivity Analysis MMRM	N LS mean (SE) Nominal p-value	42 -0.19 (0.082)	93 -0.30 (0.056) 0.2459

Source: Biometrics Reviewer's analysis

Dr. Yan notes that hierarchical testing for inferential analysis stopped due to the lack of significance in the EDSS results, and that the analysis of the mRS is presented for descriptive purposes only.

Dr. Yan questions the meaningfulness of this secondary endpoint finding in mRS because the time-to-event study design meant that some enrolled patients had 4 years of data whereas other patients would have less than 6 months at the EOS. She adds that this criticism exists for all secondary endpoints in this trial that attempt to derive a treatment effect at EOS by a change relative to baseline. Finally, she presents a summary of the mean changes in patients enrolled at a given time across the 96 weeks of the trial showing how losses due to relapses and dropouts significantly impacted the mRS mean changes in the placebo and eculizumab treatment arms, respectively, and uses these data to advance a compelling hypothesis that the analysis is flawed because the significant mRS changes are based on a small, not representative, population. Dr. Rodichok concurs and adds that, like the EDSS, the median change for mRS is 0 and of unclear clinical significance.

The following tables, copied from Dr. Yan's review, presents the results of the analysis of the change from baseline to EOS in the Hauser Ambulation Index (HAI) score and in the European Quality of Life-5 Dimension Questionnaire (EQ-5D) score.

Table 5: Analysis of Change from Baseline to EOS in the HAI

Variable	Statistic	Placebo N=47	Eculizumab N=96
Baseline HAI Score	Mean (SD) Median	2.15 (1.40) 2.0	2.38 (2.17) 2.0
Change in HAI score	Mean (SD) Median	0.51 (1.61) 0	-0.39 (1.08) 0
No change Increase (worsening) Decrease (improvement)	n (%) n (%) n (%)	31 (66.0%) 11 (23.4%) 5 (10.6%)	50 (52.1%) 9 (9.4%) 37 (38.5%)
Primary Analysis: Rank ANCOVA	Nominal p-value		0.0001
Sensitivity Analysis ANCOVA on original score	LS mean (SE) Nominal p-value	0.37 (0.201)	-0.50 (0.147) 0.0002
Sensitivity Analysis MMRM	N LS mean (SE) Nominal p-value	42 -0.26 (0.114)	93 -0.46 (0.079) 0.1021

Source: Biometrics Reviewer's analysis

Table 6 Change from Baseline to EOS in EQ-5D

Variable	Statistic	Placebo N=47	Eculizumab N=96
Baseline EQ-5D VAS Score	Mean (SD) Median	59.09 (20.39) 60.0	63.6 (20.00) 70.0
Change in EQ-5D VAS Score	Mean (SD) Median	0.57 (10.39) 0.0	5.42 (18.53) 0.0
Primary: Rank ANCOVA for VAS	Nominal p-value		0.1121
Sensitivity Analysis ANCOVA on original score	LS mean (SE) Nominal p-value	1.33 (2.57)	7.76 (1.89) 0.0302
Baseline EQ-5D Index Score	Mean (SD) Median	0.68 (0.20) 0.71	0.68 (0.20) 0.76
Change in EQ-5D Index Score	Mean (SD) Median	-0.04 (0.21) 0.00	0.05 (0.18) 0.03
Primary: Rank ANCOVA for Index	Nominal p-value		0.0021
Sensitivity Analysis ANCOVA on original score	LS mean (SE) Nominal p-value	-0.03	0.06 (0.02) 0.0075

Source: Biometrics Reviewer's analysis

Dr. Yan notes, as with the EDSS and mRS, that these analyses are reported for descriptive purposes only. Drs. Yan and Rodichok reiterate that both of these analyses of change from baseline to EOS are inherently flawed because of the lack of a uniform follow-up duration for patients enrolled in the trial. Dr. Rodichok states in his review that there was no statistical difference between treatment arms when the analysis of the HAI scores was limited to patients who had a known baseline at the start of the extension trial Study 302.

Efficacy Conclusions

This efficacy supplement to the BLA relies entirely on the efficacy findings in Study 301, a single clinical trial in patients with NMOSD who are anti-AQP4 antibody positive. 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 fulfill the criteria for providing substantial evidence for effectiveness under 21 CFR 314.126. This FDA 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.

Study 301 is an adequate, well-controlled clinical trial. The primary efficacy outcome measure, time to first on-trial relapse, is a clinically meaningful endpoint because preventing relapses in NMOSD would be predicted to improve quality of life for patients and prevent or delay disability due to these destructive attacks. The analysis of the primary efficacy endpoint yielded a large (94% reduction in relative risk) and highly statistically significant ($p<0.0001$) outcome. This primary finding was confirmed in the secondary endpoint analysis which revealed a highly statistically significant ($p<0.0001$) relative reduction of over 95% in the annualized relapse rate in patients treated with eculizumab. These two findings are extremely unlikely to be due to chance and represent a dramatic improvement over standard of care, unapproved ISTs, which fail to prevent relapses in most patients with NMOSD. Further strength to support the reliance on this single study comes from the observation that there are qualitative differences between treatment group relapses, in that there were more severe myelitis attacks in the placebo treatment group versus just a single myelitis relapse in the eculizumab treatment arm. While analyses of several of the secondary measures included to provide clinical readouts of ambulatory function and quality of life, though described nominally, did not trend toward improvement, the study was not designed in a manner that allows for an accurate estimation of disability and quality of life outcomes. The time-to-event design of the trial meant that there was not a uniform observation duration for all enrolled patients. The clinical and biometrics reviewers agreed that interpretation of the changes from baseline to end of study in any of the included measures was flawed and biased towards patients with minimal changes. Individual relapses in NMOSD can vary greatly in the extent and durability of disability meaning that a trial featuring more relapses observed over a static longitudinal treatment period would be necessary to demonstrate a treatment effect on EDSS, mRS, or other clinically relevant disability measures. Other exploratory endpoints, that were admittedly not corrected for multiplicity, such as annualized rates of hospitalization and acute treatments, trended to highly nominally significant reductions and provide further supportive evidence of benefit.

The results from Study 301 alone strongly support the effectiveness of eculizumab for the treatment of NMOSD in (b) (4) who anti-AQP4 positive without the need for confirmatory evidence. Eculizumab reduces relapse risk and frequency by approximately 94-95% relative to placebo treatment. Though the number of patients in each subgroup are too small to permit substantive analysis, another notable strength of this study is that the treatment effect of eculizumab appears consistent whether eculizumab therapy was superimposed onto several ISTs or given as monotherapy, indicating that there is an expectation that these impressive results will be sustained in the postmarketing setting in patients with NMOSD who have treatment histories spanning a broader range of ISTs. Dr. Rodichok concludes in his review that this single trial provides evidence for effectiveness of a therapy that would fulfill an unmet medical need in a rare disease population, which is a nontrivial consideration but not required considering the highly persuasive results of Study 301.

8. Safety

Dr. Rodichok's review notes that 137 patients were exposed to eculizumab in the NMOSD development program. Of these 137 patients, there were 96 patients exposed to eculizumab in the double-blind phase of Study 301 and 41 patients who were treated with placebo in the double-blind phase who subsequently received eculizumab during the open label extension Study 302. Eculizumab is FDA-approved for the treatment of PNH, aHUS, and gMG; thus, the focus of Dr. Rodichok's safety review was to confirm that there were no new or unexpected safety findings in the NMOSD population that had not already been described in the current prescribing information for the product. Dr. Rodichok also provided an analysis of the most common adverse events from Study 301 for inclusion in Section 6 of the prescribing information. Dr. Rodichok concluded that the safety database was adequate in the context of a therapy that is already approved by the FDA for indications that have similar risk/benefit considerations to NMOSD. I concur with Dr. Rodichok's conclusions.

The following are the key conclusions of the Dr. Rodichok's review of safety information contained in the BLA supplement:

- There was one death in a subject in the eculizumab treatment group in Study 301. The patient was a 30-year-old man who experienced a streptococcal pneumonia complicated by pleural effusion, congestive heart failure, sepsis, and the patient's history of recurrent history of pneumonia due to chronic obstructive pulmonary disease in the setting of chronic tobacco use. Dr. Rodichok concluded that, while eculizumab may have increased the patient's susceptibility to an infection, the patient's significant cardiorespiratory compromise unrelated to eculizumab was likely the primary cause of death.

- There were no deaths reported in Study 302.

- In Study 301, 55 Serious Adverse Events (SAEs) occurred in 30/96 (31%) patients treated with eculizumab as compared to 47 SAEs reported in 26/47 (55%) of patients treated with placebo. Based on the time of study observation, the incidence of SAEs in the group treated with eculizumab was 32.1 per 100 subject-years and 89.7 per 100 subject-years in the placebo group. The most frequently reported SAEs in both groups were NMOSD relapse events which occurred in 23/143 (16%) patients overall. When NMO relapses are excluded from total SAEs, the overall rates of SAEs reported in the eculizumab and placebo treatment groups is comparable (26.0% vs. 27.7%, respectively). SAEs from the Infestations and Infections System Organ Class (SOC) were the most frequently reported in eculizumab-treated patients 11/96 (11.5%) versus 6/47 (12.8%) in placebo-treated patients. Dr. Rodichok notes that patients in Study 301 could remain on their current immunosuppression therapy, which may explain the lack of disparity in overall rates of infections between the treatment arms. The most common infection SAE was pneumonia reported in 3/96 (3%) patients treated with eculizumab as compared to 1/47 (2.1%) of patients treated with placebo.

- Labeling for eculizumab includes a boxed warning for an increased susceptibility to serious meningococcal infections, specifically, *Neisseria meningitidis*. Dr. Rodichok notes there are no reported *Neisseria meningitidis* infections, nor any meningococcal infections, in the NMOSD development program. He notes that vaccination against *Neisseria meningitidis* was required prior to enrollment in Study 301.

- There were 3 patients who discontinued Study 301 due to adverse events (AEs), and all of these patients were from the placebo treatment arm. The reasons for discontinuing the study in these placebo-treated patients were attributed to the following AEs: pneumonia, pre-renal failure, and pancytopenia. There was 1 patient withdrawal due to death in the eculizumab treatment group as noted previously. There were 16 subjects treated with eculizumab who withdrew from Study 301, and the most common reason (in 12/16 subjects) given was "withdrawal by subject."

- Dr. Rodichok noted that infusion reactions were rare in the eculizumab group. Only 2/96 (2%) patients experienced infusion reaction AEs that led to temporary study drug interruptions.

- The following table, reproduced from Dr. Rodichok's review, summarizes the AEs with an incidence on treatment of greater than 2% that occurred more frequently than in placebo. Dr. Rodichok's analysis collects similar terms into logical groupings (e.g., leukopenia includes the terms leukopenia, neutropenia, and lymphopenia.)

Table 7: Adverse Events Reported in ≥ 2% of Patients Occurring More Frequently in Eculizumab Than Placebo Treatment

Adverse Event group	**Eculizumab**	**Placebo**
	N (%)	**N (%)**
Infection (any)	72 (75%)	32 (68%)
Upper Respiratory Infection (includes cold, rhinitis, upper respiratory tract infection, flu-like illness)	49 (51%)	16 (34%)
Infection (viral)	25 (26%)	7 (15%)
Diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-difficile	19 (20%)	9 (19%)
Eye (eye pain, eye infection, ocular disorders)	17 (18%)	6 (13%)
Dizziness, light-headedness	14 (15%)	6 (13%)
Leukopenia (neutropenia and/or lymphopenia)	12 (13%)	2 (4%)
Arthralgia, arthritis, arthrosis	12 (13%)	5 (11%)
Influenza	11 (12%)	2 (4%)

Adverse Event group	Eculizumab N (%)	Placebo N (%)
Bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	11 (12%)	4 (9%)
Constipation	9 (9%)	3 (6%)
Paresthesia, hypoaesthesia	8 (8%)	3 (6%)
Herpes virus infections	7 (7%)	3 (6%)
Anxiety, nervousness, panic attacks	7 (7%)	2 (4%)
Liver transaminases elevated (includes AST, ALT, GGT)	7 (7%)	3 (6%)
Cataract	6 (6%)	2 (4%)
Visual disturbance	6 (6%)	2 (4%)
Cellulitis, erysipelas	5 (5%)	1 (2%)
Hypertension, BP increased	5 (5%)	2 (4%)
Diabetes, glucose intolerance, hyperglycemia, Hemoglobin A1c elevated, glycosuria, ketones	5 (5%)	1 (2%)
Iron Deficiency	5 (5%)	2 (4%)
Lymphopenia	5 (5%)	1 (2%)
Cramps, muscle spasm	5 (5%)	2 (4%)
Anorexia and decreased appetite	5 (5%)	1 (2%)
Hematuria	4 (4%)	1 (2%)
Abscess, boil, furuncle	3 (3%)	1 (2%)
Weight gain	3 (3%)	1 (2%)

Source: Clinical reviewer's analysis

- Dr. Rodichok notes no safety signals of concern attributable to eculizumab that emerged from the analyses of the laboratory data or investigations (*e.g.*, electrocardiograms) obtained in Study 301.

- As noted in the OCP review, ADAs were infrequent, and there were no subjects with neutralizing antibodies identified during the trial. Dr. Rodichok notes there did not appear to be an immunogenic effect on efficacy in Study 301.

Dr. Rodichok concludes that the reported safety findings from Study 301 do not identify any new safety signals for eculizumab that are not already described in existing labeling. He recommends updating labeling to include the most common safety findings specific to NMOSD patients. This review agrees with Dr. Rodichok's conclusions.

9. Advisory Committee Meeting

This application was not referred to an Advisory Committee for review because this drug is not the first in its class, the safety profile is known because of its previous pre- and post-marketing experience in other indications, the clinical trial design was acceptable, the efficacy findings were clear, and the safety profile was acceptable considering the serious nature of the disease being treated. Current labeling makes prescribers fully aware of the risks of eculizumab, allowing them to decide whether to use this therapy and, if so, to inform patients of the incumbent risks.

10. Pediatrics

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

11. Other Relevant Regulatory Issues

- The review of this application did not identify any Good Clinical Practice (GCP) issues.
- Dr. Rodichok concludes that the applicant has adequately disclosed financial interests and arrangements with the clinical investigators.
- The Office of Scientific Investigations (OSI) did not inspect clinical sites because such inspections were not deemed necessary. No single site contributed enough enrolled patients to influence overall outcome, and the submission's data were of sufficient quality that site inspections to review original documents were not warranted.
- Soliris has a REMS for the PNH, aHUS, and gMG indications that was originally approved on June 4, 2010, to mitigate the risk of meningococcal infection and hemolysis post-discontinuation. The only change to this REMS will be to include the new NMOSD indication.

12. Labeling

Please refer to the final negotiated product label. Updates to the carton and container labeling regarding the package type term, product title, and company address were made and were consistent with the content of the prescribing information (agreed upon for S-431 and the last approved prescribing information dated April 25, 2018).

The proposed indication statement refers to the treatment of (b) (4) NMOSD who have anti-AQP4 antibodies. The diagnosis of NMOSD using current international consensus criteria do not require that patients have a positive test for anti-AQP4 antibodies to render a clinical diagnosis of NMOSD. However, at the time of the design and implementation of the pivotal trial, the diagnostic criteria for what is now termed "NMOSD" were different, and the presence of anti-AQP4 antibodies was obligatory for a diagnosis of what was then termed "NMO." Study 301 enrolled only patients who had tested positive for anti-AQP4 antibodies. (b) (4) There is presently less understanding of the role of terminal complement activation in NMOSD in the absence of anti-AQP4 antibodies. (b) (4) eculizumab should be indicated for patients with NMOSD who have tested positive for anti-AQP4 antibodies.

13. Postmarketing Recommendations

There are no postmarketing recommendations for this application. The REMS will be modified to include the NMOSD indication.

14. Recommended Comments to the Applicant

There are no additional recommended comments to the applicant.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAUL R LEE
06/27/2019 10:49:02 AM

NICHOLAS A KOZAUER
06/27/2019 10:50:49 AM

WILLIAM H Dunn
06/27/2019 11:55:45 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166s431

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125166
Priority or Standard	Priority
Submit Date(s)	12/28/18
Received Date(s)	12/28/18
PDUFA Goal Date	6/28/19
Division/Office	DNP/ODE1
Reviewer Name(s)	Lawrence Rodichok M.D.
Review Completion Date	5/27/2019
Established/Proper Name	Eculizumab
(Proposed) Trade Name	Soliris
Applicant	Alexion Pharmaceuticals, Inc.
Dosage Form(s)	Injection: 300 mg/30 mL (10 mg/mL) in a single-dose vial
Applicant Proposed Dosing Regimen(s)	900 mg IV weekly for the first 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter
Applicant Proposed Indication(s)/Population(s)	The treatment of (b) (4) Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive
Recommendation on Regulatory Action	Approval for the Treatment of Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-aquaporin-4 antibody positive
Recommended Indication(s)/Population(s)	NMOSD with Aquaporin-4 antibodies

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Glossary

AC	Advisory Committee
AE	Adverse Event
aHUS	atypical Hemolytic Uremic Syndrome
AR	Adverse Reaction
BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
COPD	Chronic Obstructive Pulmonary Disease
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Clinical Review Template
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CSS	Controlled Substance Staff
DILI	Drug-induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eCTD	electronic Common Technical Document
EDSS	Expanded Disability Status Scale
ETASU	Elements To Assure Safe Use
EQ-5D	European Quality of Life – 5 Dimension Questionnaire
EuroQOL	European Quality of Life
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FSS	Functional System Score
GCP	Good Clinical Practice
gMG	generalized Myasthenia Gravis

GRMP	Good Review Management Practice
HAI	Hauser Ambulation Index
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IRR	Infusion related Reaction
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent To Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent To Treat
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NME	New Molecular Entity
NMO	Neuromyelitis Optica
NMOSD	Neuromyelitis Optica Spectrum Disorder
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OSIS	Optic-Spinal Impairment Score
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PI	Prescribing Information or Package Insert
PK	Pharmacokinetics
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PNH	Paroxysmal Nocturnal Hemoglobinuria
PP	Per Protocol
PPI	Patient Package Insert
PREA	Pediatric Research Equity Act
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update report
RAC	Relapse Adjudication Committee
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGE	Special Government Employee
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

TI	Treating Investigator
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

Eculizumab is selective immunosuppressant (ATC code: L04AA25) humanized monoclonal antibody humanized which binds to component 5 (C5) of human complement. Eculizumab inhibits the enzymatic cleavage of C5 to activated C5 (C5a). Eculizumab is comprised of 1324 amino acids with a molecular mass of approximately 148 kiloDaltons. Eculizumab was derived from a murine monoclonal antibody (m5G1.1-mAb) that recognizes human C5.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of efficacy is demonstrated in a single adequate and well-controlled study of eculizumab compared to placebo in patients with NMOSD. Subgroup analyses of the primary endpoint supported the efficacy of eculizumab for patients who were, and for those who were not on a concurrent immunosuppressant therapy during the treatment phase of the trial. Therefore, despite the potentially confounding effect of the various concurrent immunosuppressant therapies, eculizumab has been shown to be efficacious for the reduction in relapses in NMOSD patients who are positive for the presence of anti-aquaporin 4 (AQP4) antibodies. Given the large treatment effect, the large unmet need for an effective treatment, and the rarity of NMOSD, the single trial is adequate to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

In the single adequate and well-controlled trial conducted, there was a substantial and statistically significant benefit of eculizumab treatment when measured by the time to the first relapse. The evidence of benefit on reduction of relapses is robust and therefore reliance on a single trial can be justified. The serious disability caused by NMOSD relapses and the potential for a fatal outcome from acute cervical myelitis, the rarity of the condition, and the lack of any approved therapy, also support approval based on a single adequate and well-controlled trial. Although analysis of some secondary endpoints is limited by the time-to-event design, these results are generally supportive of the primary analysis. The data on the safety of Soliris for other indications supplements the safety data from the single trial. No new safety concerns were apparent in the NMOSD trial. The primary risk in the use of Soliris, i.e. meningococcal infection, can be mitigated, but not eliminated, by the use of pre-treatment immunization, and by surveillance for all infections. The benefit to risk comparison justifies approval of the application.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• NMOSD is associated with recurrent attacks that predominantly involve the spinal cord and optic nerves • NMOSD attacks can result in severe and largely irreversible neurologic disability, including loss of independent ambulation, loss of vision, and death from respiratory failure • The spectrum of the severity of attacks in patients with NMOSD is uncertain. Although some attacks may be very severe, others may result in mild or moderate and reversible disability.	The number and severity of the attacks that occurred during the trial may have been reduced by concurrent immunosuppressant therapy. Nevertheless, any reduction in the occurrence of relapses is likely to be clinically relevant.
Current Treatment Options	• There are no approved treatments for NMOSD • Unapproved therapies currently in common use have not been studied in adequate and well-controlled studies	The unmet need for an approved therapy is large and supports approval of a therapy with a statistically significant benefit in a single adequate and well-controlled trial.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The benefit on the time to first relapse is statistically significant, even if all attacks identified by the Treating Investigator prior to adjudication are included.	The benefit demonstrated in the single trial conducted is robust and convincing.
Risk and Risk Management	• The key risk of treatment with eculizumab is the risk of infections due to interference with the complement pathway. This may be especially important for infections with encapsulated organisms, most notably Neisseria meningitidis. All subjects received immunization against meningococcal meningitis. There were no cases of meningococcal meningitis in the trial. It is uncertain if the trial represents the true incidence of these types of infection in patients with NMOSD being treated with eculizumab because of the short duration of the trial and the small number of subjects studied.	The risk of treatment with eculizumab can in part be mitigated by immunization and careful surveillance for all infections. The risk is justifiable given the clear benefit of reducing the incidence of attacks. .

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 6.1.2; **Table 37**
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 6.1.2; **Table 33**, **Table 34**
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Neuromyelitis Optica (NMO) is an inflammatory disorder of the central nervous system characterized clinically by recurrent attacks that most commonly affect the optic nerves and spinal cord. Many clinicians originally considered NMO to be an unusually severe and limited form of Multiple Sclerosis (MS). When first recognized as a distinct clinical syndrome, a diagnosis of NMO, also known as "Devic's syndrome", was considered if acute bilateral optic neuritis and acute transverse myelitis occurred concurrently or within a short period of time of each other, typically resulting in near total loss of vision and/or paraplegia. Although NMO was originally considered a monophasic illness, it was recognized that relapses were seen in up to 90% of patients. In an early review of cases of NMO from the Multiple Sclerosis program at Mayo Clinic, Wingerchuk et al.[1] expanded the "strict" definition to include cases of bilateral optic neuritis and myelitis that had occurred within 2 years of each other, and in which there was no indication of disease elsewhere in the nervous system. The group meeting the strict criteria was compared to patients who did not meet these strict criteria but whose optic neuritis attack was unilateral and/or whose attacks occurred over a period of greater than 2 years. Of the 71 patients reviewed, 23 had had a "monophasic" course, i.e. qualifying attacks occurred over a median period of 5 days with no further attacks after a minimum period of 3 years follow-up, and 48 had a "relapsing" course, i.e. there were additional attacks. The clinical characteristics of these two groups did not differ. For the relapsing group, the next attack occurred within 1 year in 55%, within 3 years in 78% and within 5 years in 90%. The severity of the attacks appeared to be much worse in comparison to MS relapses. Functional blindness and permanent monoplegia or paraplegia were not uncommon on long-term follow-up. Respiratory failure due to cervical myelitis occurred in about one-third of relapsing patients resulting in death in 15/16 patients. NMO was also distinguished from MS by the relative absence of MRI changes in the brain. A cerebrospinal fluid (CSF) pleocytosis was more common in NMO patients and oligoclonal immunoglobulin bands in the CSF were typically absent. A phase of slowly progressive disability independent of relapses is common in MS but very uncommon in NMO where disability is largely due to incomplete recovery from the individual attacks[2]. In Asia, an "optico-spinal" form accounted for up to 40% of MS but was similar clinically to NMO[3,4]. Subsequent refinements in the diagnostic criteria for NMO were based on clinical and imaging features but distinction from MS was not reliable. However, an IgG antibody that was described initially by Lennon et al.[5] , appears to be specific for patients with NMO. This antibody is not found in patients with MS. "NMO IgG" binds to aquaporin 4 (AQP4), the predominant water channel protein in the central nervous system(CNS). AQP4 is expressed prominently on astrocytic endfoot processes at the blood brain barrier in brain and spinal cord. It is also prominent in the subependymal region and in the floor of the 4th ventricle[6]. AQP4 immunoreactivity is not detectable in NMO lesions regardless of the stage of demyelination whereas this is the case only for inactive, usually chronic MS lesions. AQP4 immunoreactivity is increased at the perimeter of active areas of demyelination in MS. In NMO there may also be areas in the spinal cord and brainstem that show no evidence of demyelination but contain

eosinophil and plasma cell infiltrates with perivascular deposits of IgG, IgM and complement activation products[6]. This provides a rationale for the development of products that target either B cells or complement for the treatment of NMO. It is important to accurately distinguish NMO from MS because there are significant differences between NMO and MS in the approach to the treatment of acute attacks and the prevention of attacks. Furthermore, early intervention may be more critical for NMO because the prognosis for NMO has been considered much worse than that for MS.

A serum antibody to aquaporin 4 appears to be specific for NMO and is found in most Japanese patients with opticospinal MS who meet the clinical criteria for NMO[5]. The sensitivity of the original indirect immunofluorescence assay in clinical NMO patients was 73% (95%CI: 60-86) and specificity was 91% (79-100)[5]. For the Asian opticospinal MS, the sensitivity was 58% (30-86) and the specificity was 100% (66-100). There is wide variability in the sensitivity and specificity of the assays for anti-AQP4 antibody[7]. Some patients in whom the anti-AQP4 antibody is not found may test positive for an anti-myelin oligodendrocyte glycoprotein antibody (MOG). The clinical manifestations of CNS disease related to anti-MOG antibodies may be similar to that of NMOSD[8]. The presence of the anti-AQP4 antibody is now a key criterion in the most recent criteria for the diagnosis of NMOSD[9] (see **13.5**).

Systemic autoimmune disorders may coexist in patients with anti-AQP4 antibody positive NMOSD[10]. The most typical such autoimmune disorder is Sjögren's syndrome which may itself be associated with transverse myelitis.

2.2. Analysis of Current Treatment Options

There are no products approved for the treatment of NMOSD. Drugs that target the immune system and that are approved for indications that are perceived to be relevant to NMOSD, especially autoimmune disorders, are commonly used to treat NMOSD. Rituximab is a chimeric murine/human monoclonal antibody directed against the CD20 antigen. It is approved for the treatment of several autoimmune inflammatory disorders such as Rheumatoid Arthritis. Rituximab has been reported in uncontrolled studies to reduce the attack rate in NMOSD[11-16]. Following the initial treatment course, patients may be retreated when CD19+ cells reach a certain threshold or for recurrent attacks. Safety concerns include those typical of most drugs that suppress the immune system along with serious infusion reactions, reactivation of hepatitis B virus and the possibility of progressive multifocal leukoencephalopathy. Azathioprine (AZA) is a purine anti-metabolite approved for the treatment of RA. It has also been reported in uncontrolled studies to reduce the attack rate to nearly zero per year[17,18]. In addition to the risks due to immune suppression, AZA carries a black box warning for an increased risk of malignancies. Mycophenolate, an antimetabolite immunosuppressant generally used for suppression of rejection in transplant recipients, has also be used to prevent NMOSD relapses[18-20] with a relapse rate reduction comparable to that with AZA and rituximab.

Table 1: Available treatments for NMOSD

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
FDA Approved Treatments						
No approved treatments						
Other Treatments						
Rituximab	RA, GPA, MPA, PV*	1997	375 mg/m^2 IV qweek X4	No controlled trials	Infection, infusion reactions	
Azathioprine	RA	1968	100 mg po qd	No controlled trials	Infection, malignancy	
Mycophenolate	Transplant rejection	1995	1000 mg/day	No controlled trials	Infection, malignancy	

*: RA: Rheumatoid arthritis, GPA: Granulomatosis with polyangiitis; MPA: microscopic polyangiitis; PV: pemphigus vulgaris

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Eculizumab, has been approved as Soliris® for the treatment of:

Paroxysmal Nocturnal Hemoglobinuria: 3/16/07
Atypical Hemolytic Uremic Syndrome: 9/23/2011 (Accelerated Approval)
Atypical Hemolytic Uremic Syndrome: 4/30/14 (Regular Approval)
Generalized Myasthenia Gravis: 10/23/17

Eculizumab for the treatment of NMOSD was granted Orphan Drug Designation on June 24, 2013 (reference number 13-3987)

Soliris® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). The original REMS was approved on June 4, 2010 and has been modified multiple times since then following additional approvals, most recently following the approval for the treatment of generalized Myasthenia Gravis (gMG). The REMS is intended primarily to mitigate the risk of meningococcal infections and includes a Medication Guide, Elements to Assure Safe Use (ETASU), and a timetable for submission of assessments. ETASU include

prescriber enrollment and certification, a Patient Safety Card, Patient Safety Brochure, Dosing and Administration Guide and a dedicated internet site: www.soliris.net.

3.2. Summary of Presubmission/Submission Regulatory Activity

Original IND 116207: 1/11/13
Special protocol assessment no agreement: 2/15/13
The primary reasons for non-agreement were related to the lack of procedures for the reliable identification of relapses, the exclusion of some relapses from the primary analysis, and the need for three randomization strata: treatment naïve, previous failed IST treatment but same IST continued at randomization, previous failed IST treatment not continued at randomization
Special protocol agreement: 5/1/13
Orphan Drug Designation: 6/24/13 for the treatment of neuromyelitis optica.
Special protocol agreement rescinded: 11/21/13
The agreement was rescinded because the sponsor indicated that it was likely that there would be no treatment naïve patients in the trial. Therefore, all subjects were likely to be on concurrent, an unapproved, therapy to prevent relapses. Therefore, a positive outcome would not be interpretable without a careful review of all the study results.
Pre-BLA meeting: 12/18/2018

The studies were registered at clinicaltrials.gov: NCT01892345 and NCT02003144

3.3. Foreign Regulatory Actions and Marketing History

Eculizumab is approved for the treatment of patients ≥18 years old with Paroxysmal Nocturnal Hemoglobinuria (PNH) in multiple countries including the EU, Australia, Canada and Japan. The dose for PNH for those ≥ 18 years old is the same as that in the United States (US), i.e. 600mg weekly X 4 weeks/900mg at week 5/900mg every 2 weeks thereafter.

Eculizumab is approved for the treatment of adults with atypical Hemolytic Uremic Syndrome (aHUS) in multiple countries including the EU, Canada, Australia, and Japan. In the US, the dose for those ≥ 18 years old is 900mg/1200mg/1200mg but is weight-based for those less than 18 years old. In most non-US countries, the dose is 300mg/600mg/900mg for those ≤ 18 years old.

Eculizumab is approved for the treatment of gMG in the European Union, Japan, Iceland, Liechtenstein, and Norway. The dose in all countries is the same as for aHUS.

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

4.1. Office of Scientific Investigations (OSI)

Because no site randomized a number of subjects sufficient to influence the outcome, inspection of specific sites was not recommended.

4.2. Product Quality

Soliris is an approved product.

4.3. Clinical Microbiology

Soliris is an approved product.

4.4. Nonclinical Pharmacology/Toxicology

No new nonclinical data was submitted and, therefore, there is no nonclinical review.

4.5. Clinical Pharmacology

See the review by Drs. Krudys, Dimova and Men.

4.6. Devices and Companion Diagnostic Issues

There are no devices involved in the treatment of NMOSD with eculizumab.

4.7. Consumer Study Reviews

There are no Consumer Study Reviews.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Listing of Clinical Trials

Trial Identifier	Design	Dose regimen	Endpoints	Treatment duration	Number treated	Population	
Controlled Clinical Studies							
ECU-NMO-301	Placebo-controlled RCT	900 mg IV weekly X 4, 1200 mg IV at week 5 and q 2W thereafter	Primary: Time to first RL Secondary: ARR ΔEDSS ΔmRS ΔHAI ΔEQ5D-VAS	To first relapse or end of study	143 ECU: 96 PBO: 47	NMO and NMOSD	80 sites in 20 countries
Studies to Support Safety							
ECU-NMO-302	Open label with blinded induction	Same as study 301	Safety	Variable	121 at safety update	Completed Study 301 to relapse or EOS	70 sites in 18 countries
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
See the Clinical Pharmacology Review							

5.2. Review Strategy

The application is based on a single prospective, placebo-controlled clinical trial. A potentially problematic aspect of the trial was the permitted use of other concurrent immunosuppressants that had been continued or changed since the last relapse. In addition to assessment of the primary endpoint, the review had to assess the influence of the concurrent therapies on any apparent benefit of eculizumab therapy.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. ECU-NMO-301. A Randomized, Double-Blind, Placebo-controlled, Multi-center Trial to Evaluate the Safety and Efficacy of Eculizumab in Patients with Relapsing Neuromyelitis Optica (NMO)

6.1.1. Study Design

ECU-NMO-301 was a prospective, randomized, placebo-controlled trial of the effect of eculizumab treatment, with or without the continuation of prior unapproved immunosuppressant treatment to prevent relapses, on the time to the first on-treatment relapse compared to treatment with placebo.

Overview and Objective

The primary objective of the study was to provide substantial evidence that treatment with eculizumab was superior to treatment with placebo in patients with Neuromyelitis Optica Spectrum Disorder.

Trial Design

The study was a prospective, randomized study in which eligible patients who met the accepted criteria for a diagnosis of NMOSD were randomized to treatment with eculizumab or placebo in a 2:1 ratio. Subjects were allowed to continue treatment with specified immunosuppressant therapies (IST) provided that the dose had been stable prior to randomization and remained stable throughout the blinded treatment period. Subjects were to remain on their assigned treatment until a protocol-defined relapse occurred or until the trial was terminated at the pre-determined number of distinct adjudicated relapses. Subjects who completed the trial to a relapse or trial termination were eligible to enter an extension study of open label eculizumab treatment (OLE). Subjects who terminated the study prematurely were not eligible for the OLE.

A Screening period of from 1 to 6 weeks was allowed. Subjects had to meet all eligibility criteria and must have been vaccinated against meningococcal meningitis at least 14 days prior to receiving the first dose of study medication or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination. Rescreening was permitted if a relapse occurred during the screening period. If the patient was medically stable in the opinion of the investigator and continued to meet all eligibility criteria.

> ***Reviewer Comment: Amendment 3 (16October, 2013) removed the requirement that patients must be randomized within 30 to 90 days since the last relapse.***

Number of patients

Up to 132 patients were to be randomized at up to 150 centers.

The key eligibility criteria were:

Key Inclusion Criteria

1. Diagnosis of NMO by the 2006 criteria of Wingerchuk et al.[21] (see **13.3**) or NMOSD by the 2007 criteria of Wingerchuk et al.[22] (see **13.4**)
2. Must be NMO-IgG positive
3. Must have had at least 2 Historical Relapses[1] in the 12 months prior to screening or 3 relapses in the 24 months prior to screening.
4. Baseline Expanded Disability Scale Score (EDSS) of 7 or less (EDSS of 7: unable to walk beyond approximately 5 meters event with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair 12 hours a day)

Key Exclusion Criteria

1. Use of rituximab or mitoxantrone within 3 months of screening
2. Use of Intravenous Immune Globulin (IVIg) within 3 weeks of screening
3. Daily corticosteroid dose of no more than 20 mg of prednisone or the equivalent per day

[1] Historical relapses are the relapses that occurred prior to the Screening Visit, including the first NMO attack. For this protocol, historical relapse is defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change on neurologic examination (clinical findings or magnetic resonance imaging [MRI] findings or both) that persisted for more than 24 hours and/or the new onset of neurologic symptoms or worsening of existing neurologic symptoms that required treatment. Treatment is defined as use of high-dose IV steroids, PE or IVIg. Events that occur within a 30-day interval are considered as one relapse (Protocol Section 7.4.1).

4. Unresolved meningococcal disease
5. Any systemic bacterial or other infection which is clinically significant in the opinion of the Investigator and has not been treated with appropriate antibiotics

See **13.6** for the complete list of eligibility criteria

Eligible patients were randomized on Day 1 to treatment with either eculizumab or placebo in a 2:1 ratio. Randomization was stratified by EDSS score at randomization (≤ 2.0 and ≥2.5 to <7.0) and by IST status (treatment naïve, continuing on the same IST since last relapse (dose changes allowed), changed or added IST since last relapse).

- Treatment naïve patients were defined as those who have received or are receiving either no IST or have received only corticosteroids following treatment of acute relapses prior to the screening.

- Patients continuing on the same IST(s) for relapse prevention since the last relapse were defined as those who previously received IST(s) other than only corticosteroids alone and were continuing on the same IST(s) since the most recent relapse at the time of randomization. Patients who had dose adjustment with the same IST(s) following a relapse were included in this group.

- Patients with changes in IST(s) used for relapse prevention since the last relapse were defined as those who at the time of randomization had started a new IST, added another IST, or withdrew any IST(s) since the last relapse.

Reviewer Comment: There is an important distinction between those who were treatment naïve, as defined above, and those who were not being treated with a concurrent IST at baseline.

Dose rationale

Based on results from trials for the treatment of aHUS, free C5 concentration was reduced significantly with increasing concentrations of eculizumab beginning at >50 µg/mL and was at near zero levels with eculizumab concentrations above 100 µg/mL. The weekly doses of 900 mg during the induction phase and the maintenance dose of 1200 mg every 2 weeks were expected to result in over 90% inhibition of free C5 levels.

Treatment of Subjects

Eculizumab (600 mg, 900 mg or 1200 mg) or matching placebo was administered IV over approximately 35 minutes according to the regimen in the table below.

Table 3: Investigational Product Dosage and Administration

Dose Period	Frequency of Investigational Product (IP) Administration	Visit #	# of Vials	Equivalent Eculizumab Dose
Induction Phase	Weekly (every 7 ± 2 days)	2-5	3	900 mg
		6	4	1200 mg
Maintenance Phase	Every 2 weeks (14 ± 2 days) from the fifth dose onward	7 – EOS/ET	4	1200 mg
Supplement Doses*	If PE is given for On-Trial Relapse, administer after each PE as described below*.		2	600 mg

Induction Phase

Nine hundred (900) mg of eculizumab were administered weekly x 4 (every 7 days ±2 days, Visits 2-5 [Day 1 – Week 3]) followed by 1200 mg of eculizumab one week later (7 days ±2 days) for the 5th dose (Visit 6 [Week 4]).

Maintenance Phase

The maintenance dose was 1200 mg of eculizumab every two weeks (14 days ±2 days)

*Supplemental Doses

If a subject was treated with Plasma Exchange (PE) for an On-Trial Relapse on a day that IP administration is not routinely scheduled during the Study Period, a supplemental dose of 600 mg of eculizumab was administered after each PE, preferably within 1-2 hours. If PE is administered on a day of regularly scheduled IP administration, patients received the regularly scheduled dose after each PE, preferably within 1-2 hours.

Recommended Standardized Relapse Treatment

Treatment for a relapse was at the discretion of the Treating Physician. The recommended acute treatment for a relapse was:

1. One gram IV methylprednisolone administered daily for 3-5 days followed by an oral prednisone tapering.

2. If there was no or minimal response to methylprednisolone, PE was allowed at the discretion of the Treating Physician. Five cycles of PE that each removed 1.0-1.5 volumes of circulating plasma was recommended.

Concomitant Medications

Immunosuppressive agents, such as azathioprine (AZA), mycophenolate mofetil (MMF),

methotrexate, tacrolimus, cyclosporine or cyclophosphamide either in combination or mono-therapy were permitted. Changes in the dose of these drugs during the trial were not permitted.

> ***Reviewer Comment: At the pre-BLA meeting the sponsor indicated that changes in the dose of concomitant ISTs were indicated as minor protocol violations and changes for efficacy, e.g. for the occurrence of a relapse, were considered a major violation and such subjects were excluded from the per-protocol analysis.***

The following medications were prohibited during the trial:

Concomitant use of rituximab with eculizumab was contraindicated

- Mitoxantrone
- Immunomodulatory therapies including: interferon beta-1b; interferon beta-1a and glatiramer acetate
- Other biologic agents such as tocilizumab
- IVIg for relapse prevention
- PE for relapse prevention

Key Assessments (see **13.6** for complete schedule of assessments)

See **13.8** for details regarding the EDSS

See **13.9** for details regarding the OSIS

See **13.10** regarding the HAI

See **13.11** for the mRS

Screening

Complete physical and neurologic examination
ECG
Pregnancy test
NMO-IgG
EDSS
Snellen chart
Neisseria meningitidis vaccination

Study period

Subjects were randomized on Day 1 followed by weekly visits during the induction phase and then every 2 weeks to week 96.

EDSS, mRS, HAI, EuroQol (EQ-5D), SF-36, Snellen chart, C-SSRS, neurologic examination: Day 1, week 4, 8, 12, 24, 36, 48, 60, 72, 84, 96 and every 12 weeks to EOS or early termination visit
Optic Spinal Impairment Score (OSIS): Day 1
ECG: Week 52, 96, EOS or early termination visit
Safety laboratory studies, pregnancy test: Day 1, week 4, 8, 12, 24, 36, 48, 60, 72, 84, 96 and every 12 weeks to EOS or early termination visit
NMO IgG: Day 1, week 4, 8, 12, 24, 36, 48, 60, 72, 84, 96 and then every 12 weeks to EOS or early termination visit

Reviewer Comment: The NMO IgG was collected at the site and sent to a central laboratory. However, the laboratory or laboratories performing the test were not specified. In response to a request at the pre-BLA meeting, the sponsor has provided a listing of the study subjects with the analysis method and laboratory for the NMO IgG result at Screening.

Treating physician

The Treating physician was responsible for overall management of the subject, including determination of eligibility, supervision of administration of the investigational product, and collection and documentation of all adverse events. S/he did have access to the results of laboratory study results. In the event of a relapse, following completion of all relapse assessments, the Treating Physician was responsible for acute treatment of the relapse and any subsequent changes in therapy to prevent future relapses.

Blinded EDSS rater

EDSS scores were to be determined by a qualified person who could not be the Principle Investigator, sub-investigator or otherwise involved in the subject's care. All raters were to receive specific training on the EDSS scale. Non-physician raters could be used but had to be approved by the sponsor.

Table 4: Responsibilities of Treating Physician and EDSS rater

Treating Physician	EDSS Rater
Blinded to the patient's treatment assignment: • Determine patient eligibility for the trial • Overall patient management during the trial, including IP administration and safety assessments. • Perform mRS* • Perform Columbia-Suicide Severity Rating Scale (C-SSRS)* **At the time of relapse**: • Initial patient assessment • Have the EDSS Rater record FSS and EDSS score* • Perform a complete neurologic examination • Determine if the patient has experienced an On-Trial Relapse • Determine relapse severity by OSIS • Assess VA, Snellen Chart* • Assess ambulation by HAI* • Have the patient complete the EQ-5D and Short Form Health Survey (SF-36)* • Treat relapse	**Blinded to all other trial data as well as all other patient clinical chart data:** At protocol specified time points: • Kurtzke neurological assessment • Document FSS • Record EDSS score **At the time of relapse:** • Perform the Kurtzke neurologic assessment • Document FSS • Record EDSS score

*: could be performed by the Treating Physician or his/her designee.

Relapse assessment

Subjects were instructed to notify the study site at the first symptom or sign of a potential relapse. An evaluation was to be conducted no later than 48 hours after notification. All reports of a possible relapse were to be recorded in the electronic Case Report Form (eCRF). All potential relapses were to be evaluated by the Treating Physician and the EDSS rater. For each Relapse Evaluation Visit, the blinded rater was to record the EDSS and Functional System Scores (FSS). The Treating physician was to conduct a complete neurologic examination and OSIS. Either the Treating physician or appropriately trained designee was to assess visual acuity using the Snellen Chart and record the HAI.

Table 5: Schedule of Assessments for a relapse evaluation visit

Assessment	Relapse Evaluation Visit	Follow- Up Relapse Evaluation Visits			
Trial Week	**Within 24-48 hours**	**+W1**	**+W4**	**+W6/EOS**	**Unscheduled**
Physical Examination				X	
Weight				X	
Vital Signs	X	X	X	X	X
Electrocardiogram (ECG)				X	
Concomitant Medication	X	X	X	X	X
Adverse Events (AEs)	X	X	X	X	X
Clinical Laboratory Tests	X			X	X
Pregnancy test (serum)				X	X
NMO-IgG (serum)	X			X	X
NMO-IgG (CSF)	X			X	X
HAHA (serum)				X	
PK/PD/Free C5 (serum)	T/P	T/P	T/P	T/P	T/P
PK/Free C5 (CSF)	X			X	X
EuroQol (EQ-5D)				X	X
Short Form Health Survey (SF-36)				X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)				X	X
Expanded Disability Status Scale (EDSS)	X	X	X	X	X
Modified Rankin Scale (mRS)				X	
Patient Education Card and NMO Symptom Evaluation	X	X	X	X	X
Neurologic Examination	X	X	X	X	X
Optic Spinal Impairment Score (OSIS)	X	X	X	X	X
Snellen chart	X	X	X	X	X
Hauser Ambulation Index (HAI)	X	X	X	X	X
Medically indicated tests	X	X	X	X	X
N. meningitidis vaccination					
Patient Safety Identification Card	X	X	X	X	X
Investigational Product (IP) Infusion	Continue every 1-2 weeks (± 2 days) as scheduled				

An On-Trial Relapse was defined as any new onset or worsening of previous neurologic symptoms with an objective change on neurologic examination that persisted for 24 hours or more, and attributable to NMOSD and not due to an alternate identifiable cause such as an infection, excessive exercise or high ambient temperature. The Treating physician made the determination of whether the event met the protocol definition of an On-Trial Relapse. The Treating physician determined the appropriate acute treatment for the relapse, including whether to change any concurrent IST. The severity of the relapse was determined using the OSIS assessments as conducted by the Treating Physician.

Amendment 9 (1July2016) revised the determination of an On-Trial relapse from investigator determination only to review and adjudication by an independent Adjudication Committee.

> ***Reviewer Comment: In response to an Additional Information Request, the sponsor indicated that Amendment 9/protocol version 6.0 was implemented on 1July, 2016 at which time 93 subjects had been randomized and 23 adjudicated attacks had occurred. Over the next 2 years no further initial attacks had occurred and the study was terminated prematurely on 24 May, 2018 at 23 attacks rather than the planned 24 attacks***

Adjudication of Relapses

The relapse adjudication committee consisted of three neurologists or neuro-ophthalmologists external to the sponsor and blinded to treatment assignment. The committee reviewed all On-Trial Relapses. The decision was by majority vote.

> ***Reviewer Comment: The rationale for the initiation of an adjudication process is provided in the summary of changes for Amendment 9. The sponsor states that there was "variability observed across sites in the diagnosis of relapse events" and that some of the relapses that had been identified "could be queried on independent medical review".***

Cases of Interest (COI)

To identify all possible relapses, the sponsor added the concept of a "case of interest". This was defined as:

A patient who was seen by the Treating Physician for a relapse evaluation within the protocol-defined 24-48 hour interval but determined not to have a relapse
OR
A patient with a "sentinel" adverse event such as weakness, sensory symptoms, reduction in

visual acuity
AND
An MRI that was performed as part of the evaluation of either of the above events
OR
Neurologic symptoms that were treated
OR
Contemporaneous worsening of the neurologic exam recorded by the Treating Physician

All COI were sent to the Relapse Adjudication Committee for review

> ***Reviewer Comment: The sponsor reported the above process at the pre-BLA meeting. It is not included in the protocol or the Statistical Analysis Plan.***

Safety Assessments

Generally accepted clinical definitions of adverse events were used during the trial. The reporting period for SAEs was from the time consent was signed to 8 weeks after the last dose of IP. Non-serious AEs were reported from the first dose of IP to the last study visit. There were no specified AEs of special interest. An independent data monitoring committee (IDMC) monitored unblinded safety data at regular intervals.

Safety follow-up visit

Subjects who received any dose of IP and who discontinued treatment prematurely or who completed the study but did not enter the open label extension study were assessed 8 weeks after the last dose of IP.

Study Endpoints

Primary Endpoint

Time to the first adjudicated on-trial relapse (prior to amendment 9 the primary endpoint was time to first on-trial relapse).

Secondary Endpoints (taken from SAP version 5.0, 01June2018)

1. Adjudicated annualized relapse rate
2. Change from baseline in EDSS score at the EOS
3. Change from baseline in mRS score at the EOS
4. Change from baseline in ambulatory function as measured by HAI at EOS
5. Change from baseline in EQ-5D at the EOS

Statistical Analysis Plan

The sample size of 132 subjects was based on the assumption of a 40% relapse-free rate in the placebo group and a hazard ratio of 0.24 using the log-rank test for the comparison of eculizumab to placebo for the primary analysis. That would yield a power of 90%. The final plan was to observe 24 adjudicated relapses in 24 subjects.

The primary analysis population was to be the "Full Analysis Set" (FAS) defined as all subjects who were randomized and who had at least one dose of IP.

Analysis of the primary endpoint was to be stratified by EDSS score at baseline (≤2 vs. ≥2.5) and by the IST status group at randomization. Subjects who had a relapse that was confirmed, but not within 24-48 hours, were to be censored based on the subject's last date in the study. Additional analyses were planned for those relapses that were confirmed but by more than 48 hours after the initial report.

> ***Reviewer Comment: Because of the potentially confounding effect of the use of concomitant and unapproved immunosuppressant therapies, the Division requested subgroup analyses by the major concomitant ISTs.***

The secondary endpoints were to be analyzed in a closed sequential hierarchy in the order listed above. For the change in EDSS or mRS from baseline to EOS, the last EDSS or mRS was considered to be the EDSS or mRS at the end of the post-relapse assessment period or at the end of treatment for those who did not have a relapse.

Protocol Amendments

Version 1.0 – 31December, 2012
Version 2.0 – 15March, 2013
Version 3.0 – 15May, 2013
- Amendment 1, version 3.1 – minor changes – 21June, 2013
- Amendment 2, version 3.2 – minor changes (Japan only) – 10July, 2013

Version 4.0 – 16October, 2013
- Amendment 3, version 4.0 - 16October, 2013
  - Increased the number of sites from 100 to 120
  - Changed the requirement for the history of relapses for eligibility from
    - 2 relapses in the last 6 months or 3 relapses in the last 12 months with the most recent attack occurring more than 30 days and less than 90 days prior to randomization

    to
    - 2 relapses in the last 12 months or 3 relapses in the last 24 months with

at least one relapse in the 12 months prior to Screening

- Removed the requirement for randomization within 30 to 90 days from most recent relapse
- Allowed Treating Physician to define a "stable" dose of permitted concurrent immunosuppressant drug
- Changed the criteria for termination of the trial from
  - the result of an interim analysis or
  - the maximum number of 29 relapses

  to
  - the maximum number of 24 relapses or
  - 132 patients enrolled
- Added cyclosporine to permitted ISTs
- Revised randomization stratification related to prior IST treatment from
  - Treatment naïve vs. prior IST and receiving IST at randomization vs. prior IST and not receiving IST at randomization

  to
  - Treatment naïve vs. continuing same IST since last relapse vs. changes in IST since last relapse
- Extended Safety follow-up period to 8 weeks
- Changed the exclusion for the use of rituximab and mitoxantrone from 3 months prior to randomization to 3 months prior to screening
- Added an exclusion for patients being treated with >20 mg prednisone (or the equivalent) prior to Screening; required the same during the trial.
- Added a possible interim analysis at 17 relapses in 17 distinct subjects

Amendment 4 – version 4.1 – 27December2013 - Japan only - comparable to Amendment 3

Amendment 5 – version 4.2 – 16December2014 - Czech Republic only – removal of PK and CSF sampling

Version 5.0

Amendment 6 – version 5.0 - 25February2015

- Removed requirement for a positive NMO-IgG at screening to allow "historically positive" NMO-IgG
- Allow non-physicians to conduct EDSS assessments
- Expanded the number of sites to 150
- Remove the planned interim analysis
- Extended the screening period from 1 to 3 weeks to 1 to 6 weeks

Amendment 7 – version 5.1 – 2April2015 – changes as in amendment 6 – for Japan

Amendment 8 – version 5.0 – 17April2015 – changes as in amendment 6 – Czech Republic

Version 6.0 – 1July, 2016

Amendment 9 – version 6.0 – 1July2016

- Changed the determination of On Trial relapse from investigator determination to review and adjudication by an independent Adjudication Committee
- Primary endpoint changed to Time to Adjudicated On-Trial Relapse

Amendment 10 – 14July2016 – changes as in Amendment 9 – Japan
Amendment 11 – 14July2016 – changes as in Amendment 9 – Czech Republic
Amendment 12 – 14July2016 – changes as in Amendment 9 – Thailand

6.1.2. Study Results

Compliance with Good Clinical Practices

Nineteen sites, all in the United States, conducted the study under the IND. Fifty-one sites did not conduct the study under the IND, all outside the US. The sponsor provided the following attestation:

"The studies were undertaken in accordance with Alexion standard operating procedures, which comply with the principles of GCP. The studies were conducted with the approval of ECs or IRBs. Informed consent was obtained for all patients, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Regulatory approval was obtained from the relevant health authorities."

Financial Disclosure

The sponsor provided a listing of sites with and without a financial interest of $25,000 or more. There was one such site in the US, site (b) (6) at (b) (6) The site randomized 3 patients, 2 to eculizumab and one to placebo. Both subjects were censored for the primary endpoint analysis. The second site with a financial interest was site (b) (6) at the (b) (6). The site randomized 2 patients, both to placebo. One had a relapse and one was censored for the primary endpoint analysis.

> ***Reviewer Comment: One site randomized 5 patients, two sites randomized 4 patients and the remainder randomized 3 or less. Considering the robustness of the treatment effect, no single site could have influenced the key study results.***

Patient Disposition

Date first patient enrolled: 11 Apr 2014
Date last patient completed: 17 Jul 2018

There were 18 patients who were screen failures initially and were rescreened and eventually

randomized. This was permitted by protocol.

One-hundred forty-three (143) subjects were randomized 2:1 to eculizumab (n=96) or placebo (n=47) at 70 sites in America, Asia-Pacific and the European Union. Three sites randomized 5 subjects, 4 randomized 4 subjects and 15 sites randomized 3 subjects. The actual randomization ratio was approximately 2:1 in each major region.

Table 6: Randomization by Geographic Region

Geographic Region 1	Eculizumab	Placebo	Subjects(filtered)
Europe	32 (62.7%)	19 (37.3%)	51 (100.0%)
Asia-Pacific	35 (72.9%)	13 (27.1%)	48 (100.0%)
Americas	29 (65.9%)	15 (34.1%)	44 (100.0%)
Subjects(filtered)	96 (45.1%)	47 (22.1%)	213 (100.0%)

Source:JRevADSLTRT01PbyGeoRegrowpercentfilterRANDFL_Y.xls

Reviewer Comment: Randomization at the 22 sites that enrolled 3 or more subjects was not well balanced. These sites randomized 76 subjects, 59 to eculizumab and 17 to placebo (3.47:1). The remaining 48 sites randomized 67 subjects, 37 to eculizumab and 30 to placebo (1.23:1).

Table 7: Overall disposition

Category for Disposition Event	Standardized Disposition Term	(missing)	Eculizumab	Placebo	Subjects
Protocol Milestone	Informed Consent Obtained	70 (100.0%)	96 (100.0%)	47 (100.0%)	214 (100.5%)
	Screen Failure*	70 (100.0%)	8 (8.3%)	9 (19.1%)	88 (41.3%)
	Randomized	0 (0.0%)	96 (100.0%)	47 (100.0%)	143 (67.1%)
Disposition Event	Completed	0 (0.0%)	80 (83.3%)	44 (93.6%)	124 (58.2%)
	Withdrawal by Subject	0 (0.0%)	12 (12.5%)	1 (2.1%)	13 (6.1%)
	Lost to Follow-Up	0 (0.0%)	3 (3.1%)	0 (0.0%)	3 (1.4%)
	Adverse Event	0 (0.0%)	0 (0.0%)	2 (4.3%)	2 (0.9%)
	Death	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (0.5%)
	Total Subjects (Filtered)	70 (100.0%)	96 (100.0%)	47 (100.0%)	213 (100.0%)
Other Event	Unblinded By Site	0 (0.0%)	1 (1.0%)	1 (2.1%)	2 (0.9%)
					(Denom=ColTot)

*: 22 subjects were rescreened once, 16 of whom were randomized (8 to eculizumab and 8 to placebo); 2 subjects were rescreened twice, 2 of whom were randomized (one to each treatment arm).

Source: JRev 301 DSCATbyDSDECODbyTRT01P.xls

Reviewer Comment: Informed consent was obtained 239 times in 213 potential subjects. 189 signed informed consent once - 87 were randomized to eculizumab,

38 to placebo and 64 were considered screen failures. Of the latter 64 potential subjects, 22 signed consent a second time and 8 of those were randomized to eculizumab and 8 to placebo – 6 were screen failures a second time and were never randomized. Consent was signed 3 times in 2 potential subjects and each was randomized, one to eculizumab and one to placebo.

Screen failures

The most common causes of screen failure were AQP4-Ab negative (45 instances in 42 patients), not meeting the requirements for historical relapses (11 instances in 11 patients), EDSS not 7 or less (6 instances in 5 patients), Investigator decision (5 instances in 5 patients), and corticosteroid dose greater than 20 mg per day at screening (3 instances in 3 patients).

Disposition Events

The proportion of subjects who completed the trial was 83.3% in the eculizumab group and 93.6% for the placebo group (Table 7 above). Subjects were considered to have completed the trial if they completed to the end of the study without a relapse or if a relapse occurred, as determined by the Treating Investigator. For those who did not have a relapse, the end of the study was defined as the time that the study was terminated for reaching the required number of relapses. The study ended at a relapse for 66% of the subjects being treated with placebo and for 19% of those treated with eculizumab.

Table 8: Completion details

Complete Details	Eculizumab	Placebo	Subjects
Completed Eos	65 (81.3%)	15 (34.1%)*	80 (37.6%)
Completed Relapse	15 (18.8%)	29 (65.9%)	44 (20.7%)
Subjects	80 (100.0%)	44 (100.0%)	213 (100.0%)
			(Denom=ColTot)

Source: JRev 301 DSCOMPbyTRT01PfilterCOMPLFL_Y.xls

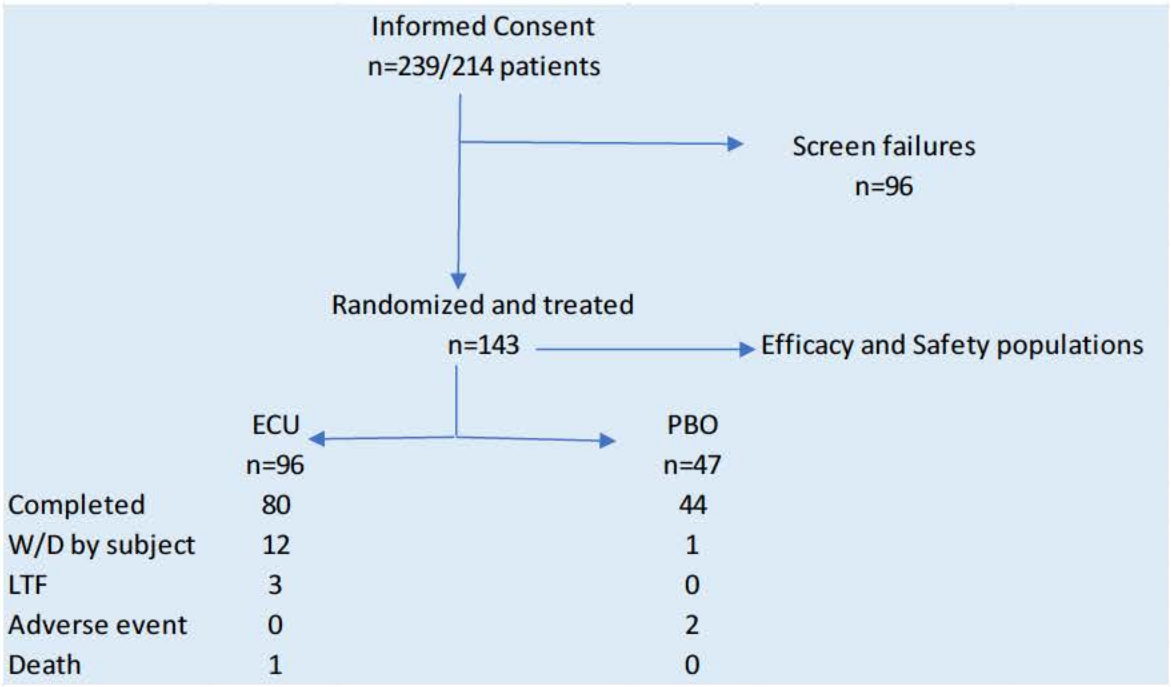
*: This includes 1 patient who experienced a relapse that was outside of the analysis window defined for an "On-trial Relapse"; this relapse is not considered an On-trial Relapse in the efficacy analyses.

Premature Discontinuation

Sixteen of 96 subjects being treated with eculizumab did not complete the study compared to 3 of 47 treated with placebo. The most common reason for failure to complete for the eculizumab group was "withdrawal by subject". There was only one withdrawal by subject in the placebo group. The 12 eculizumab subjects withdrew at mean study day 467±250 (range 106-835; median 364). The placebo subject withdrew at day 366.

Reviewer Comment: Although there were a disproportionate number of withdrawals by subject in the eculizumab group, a review of the CRFs and the additional information in Table 15 of the CSR for the 12 instances of withdrawal by subject in the eculizumab group does not reveal any indication that these events were related to eculizumab, relapses or adverse events.

Figure 1: Study 301: Diagram of disposition



Protocol Violations/Deviations

Approximately 40% of randomized subjects had one or more major protocol deviations. Major deviations were those that involved not meeting key eligibility criteria, not receiving at least 80% of the required dose of IP while in the Study Period, taking a prohibited medication during the study period prior to a relapse, a change in dose or addition of an IST during the study period and prior to a relapse, emergency unblinding and other deviations that were deemed to have the potential to affect efficacy.

Table 9: Major protocol deviations by treatment group

Protocol Deviation Coded Term	Eculizumab		Placebo		Subjects total	
	N=96		N=47		N=143	
Concomitant Medication	5	5.2%	1	2.1%	6	4.2%
Eligibility Criteria	2	2.1%	1	2.1%	3	2.1%
Informed Consent	13	13.5%	9	19.1%	22	15.4%
Investigational Product	9	9.4%	1	2.1%	10	7.0%
Randomization	9	9.4%	6	12.8%	15	10.5%
Safety Reporting	7	7.3%	4	8.5%	11	7.7%
Source Document	5	5.2%	1	2.1%	6	4.2%
Study Procedures/Tests	11	11.5%	3	6.4%	14	9.8%
Visit Schedule	7	7.3%	8	17.0%	15	10.5%
Subjects total	37	38.5%	20	42.6%	57	39.9%

Source: JRevDVCODbyTRT01PfiltRANDFL_YandDVCAT_Major v2.xls

Reviewer Comment: A key potential factor that could confound the key efficacy results was a change in the status of the concomitant IST during the blinded treatment phase of the trial. These were included under major deviations/concomitant medications. There were 5 such deviations in the eculizumab group – 4 of the 5 were a reduction in a concomitant IST or corticosteroid and therefore would most likely not have positively affected the occurrence of relapses. The one such deviation in the placebo group was due to the administration of 1000mg methylprednisolone IV which could have suppressed relapses but would not have favored eculizumab.

A review of all of the other major deviations did not reveal any that would have an impact on interpretation of the study results.

Treatment assignment was unblinded for two subjects:

Subject (b) (6) was randomized to eculizumab. This subject voluntarily withdrew from treatment at 70 days of treatment, 8 infusions, 86 days of study period and 106 days on study. The reason for withdrawal was unknown. This subject did not have a relapse. This subject was hospitalized for an SAE of head contusion on (b) (6) study day 240)

Subject (b) (6) was randomized to placebo. The drug was withdrawn for severe pancytopenia on (b) (6)

Demographics

The demographics of the ITT population for Study NMO-ECU-301 are listed in Table 10 below. As expected for patients with NMOSD, 90% of subjects were female. Approximately 25% of subjects were over 55 years old. Approximately 50% were white; Asians represented about 35% of the population. Approximately 10% of the subjects were of Japanese descent. The key demographic characteristics of subjects with NMO did not differ significantly from those with NMOSD. The key demographics are generally balanced by treatment arm.

Table 10: Demographics ITT Study NMO-ECU-301

Subgroup	Eculizumab (N = 96) n (%)	Placebo (N = 47) n (%)	Total (N = 143) n (%)
Sex			
Female	88 (91.7)	42 (89.4)	130 (90.9)
Male	8 (8.3)	5 (10.6)	13 (9.1)
Age			
Mean	43.83	45.04	44.23
Standard Deviation	13.36	13.25	13.29
Minimum	19	21	19
Median	44.5	44	44
Maximum	70	75	75
Age Group			
Age Group 1 (18 <= AGE <= 55)	72 (75.0)	37 (78.7)	109 (76.2)
Age Group 2 (55 < AGE < 90)	24 (25.0)	10 (21.3)	34 (23.8)
Race			
American Indian or Alaska Native	1 (1.0)	0 (0.0)	1 (0.7)
Asian	37 (38.5)	15 (31.9)	52 (36.4)
Black or African American	9 (9.4)	8 (17.0)	17 (11.9)
Missing	2 (2.1)	0 (0.0)	2 (1.4)
Other	1 (1.0)	0 (0.0)	1 (0.7)
White	46 (47.9)	24 (51.1)	70 (49.0)
Ethnicity			
Hispanic or Latino	13 (13.5)	3 (6.4)	16 (11.2)
Missing	5 (5.2)	3 (6.4)	8 (5.6)
Not Hispanic or Latino	78 (81.2)	41 (87.2)	119 (83.2)
Region			

Subgroup	Eculizumab (N = 96) n (%)	Placebo (N = 47) n (%)	Total (N = 143) n (%)
Asia	40 (41.7)	16 (34.0)	56 (39.2)
Europe	25 (26.0)	15 (31.9)	40 (28.0)
Other	2 (2.1)	1 (2.1)	3 (2.1)
South America	5 (5.2)	1 (2.1)	6 (4.2)
United States	24 (25.0)	14 (29.8)	38 (26.6)

Source: OCS Demographics Tool using DEM and ADSL. Custom age grouping.

Medical History

In general, the medical history for the study subjects was unremarkable as listed in Table 11.

Table 11: Medical History Dictionary Derived Term occurring in 10% or more of either treatment group

Dictionary Derived Term	Eculizumab	Placebo
Constipation	27 (28.1%)	17 (36.2%)
Menopause	22 (22.9%)	7 (14.9%)
Depression	19 (19.8%)	9 (19.1%)
Hypertension	18 (18.8%)	9 (19.1%)
Gastro-oesophageal reflux disease	18 (18.8%)	7 (14.9%)
Insomnia	15 (15.6%)	7 (14.9%)
Drug hypersensitivity	15 (15.6%)	6 (12.8%)
Anxiety	14 (14.6%)	7 (14.9%)
Urinary tract infection	10 (10.4%)	10 (21.3%)
Hypothyroidism	10 (10.4%)	7 (14.9%)
Anaemia	10 (10.4%)	5 (10.6%)
Blindness unilateral	10 (10.4%)	5 (10.6%)
Hysterectomy	8 (8.3%)	6 (12.8%)
Osteoporosis	12 (12.5%)	2 (4.3%)
Hyperlipidaemia	11 (11.5%)	3 (6.4%)
Diabetes mellitus	9 (9.4%)	4 (8.5%)
Migraine	7 (7.3%)	5 (10.6%)
Appendicectomy	11 (11.5%)	0 (0.0%)
Herpes zoster	4 (4.2%)	7 (14.9%)
Headache	5 (5.2%)	6 (12.8%)
Systemic lupus erythematosus	4 (4.2%)	6 (12.8%)
Fatigue	3 (3.1%)	5 (10.6%)

Source: JRevADSL RANDFL_Y MHDECODbyTRT01P.xls

There was an increased incidence of other autoimmune disorders in patients with NMOSD. Table 12 lists the autoimmune disorders reported by Study 301 subjects.

Table 12: Autoimmune disorders at baseline, ITT

Dictionary Derived Term	Eculizumab	Placebo
Blood and lymphatic system disorders		
Antiphospholipid syndrome	1 (1%)	1 (2 %)
Immune thrombocytopenic purpura	1 (1%)	0 (0.0%)
Autoimmune haemolytic anaemia	1 (1%)	0 (0.0%)
Endocrine disorders		
Autoimmune thyroiditis	6 (6%)	1 (2%)
Hepatobiliary disorders		
Lupus hepatitis	0 (0.0%)	1 (2%)
Immune system disorders		
Sarcoidosis	1 (1%)	0 (0.0%)
Musculoskeletal and connective tissue disorders		
Systemic lupus erythematosus	4 (4%)	6 (13%)
Rheumatoid arthritis	5 (5%)	2 (4%)
Sjogren's syndrome	4 (4%)	3 (6%)
Scleroderma	1 (1%)	0 (0.0%)
Skin and subcutaneous tissue disorders		
Psoriasis	1 (1%)	1 (2%)
Nervous System disorders		
Myasthenia gravis	2 (2%)	0 (0%)

Source: MH Immune disorders.xlsx

This incidence of various anemias and cytopenias that might be relevant to the safety of eculizumab is listed in Table 13.

Table 13: Anemias and cytopenias at baseline, ITT

Dictionary Derived Term	Eculizumab	Placebo
Anaemia	10 (10%)	5 (11%)
Leukopenia	2 (2%)	3 (6%)
Neutropenia	2 (2%)	2 (4%)
Thrombocytopenia	0 (0%)	3 (6%)
Pancytopenia	2 (2%)	0 (0%)
Agranulocytosis	1 (1%)	0 (0%)
Autoimmune haemolytic anaemia	1 (1%)	0 (0%)
Cytopenia	1 (1%)	0 (0%)

Source: JRevADSL RANDFL_Y MHDECODbyTRT01PfiltMHBODSYS_BloodLymph.xls

Concomitant Medications at Screening

The use of immunosuppressant therapies for the prevention of relapses is presented in the section on Baseline Disease Characteristics below. The concomitant medications at the time of screening are listed by the World Health Organization code level 1 in Table 14 below.

Table 14: Concomitant medications at screening, WHO level one, randomized population

WHO DD ATC Text Level 1	Eculizumab	Placebo
Alimentary Tract and Metabolism	10 (10.4%)	4 (8.5%)
Antiinfectives For Systemic Use	86 (89.6%)	38 (80.9%)
Blood and Blood Forming Organs	8 (8.3%)	1 (2.1%)
Cardiovascular System	1 (1.0%)	0 (0.0%)
Dermatologicals	1 (1.0%)	4 (8.5%)
Genito Urinary System and Sex Hormones	4 (4.2%)	5 (10.6%)
Musculo-Skeletal System	7 (7.3%)	1 (2.1%)
Nervous System	14 (14.6%)	8 (17.0%)
Respiratory System	0 (0.0%)	1 (2.1%)
Sensory Organs	2 (2.1%)	0 (0.0%)
Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	9 (9.4%)	4 (8.5%)
Various	1 (1.0%)	1 (2.1%)
Subjects	96 (100.0%)	47 (100.0%)

Source: JRevselADSLRANDFL_Y ATCTX1byTRT01AfiltEPOCH_SCR.xls

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The diagnosis of NMO or NMOSD was based the 2007 criteria of Wingerchuk[21,22]. By those criteria, a diagnosis of "definite NMO" required the following[21]:

- Optic Neuritis
- Acute Myelitis
- At least two of three supportive criteria
    - Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
    - Brain MRI not meeting diagnostic criteria for multiple sclerosis
    - NMO IgG seropositive status

A diagnosis of Neuromyelitis Spectrum Disorder[22] included the following:

- Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord lesion seen on MRI)
- Optic neuritis: recurrent or simultaneous bilateral
- Asian optic-spinal multiple sclerosis
- Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease
- Optic neuritis or myelitis associated with brain lesions typical of neuromyelitis optica (hypothalamic, corpus callosal, periventricular, or brainstem)

Based on the above definitions, subjects in trial 301 were considered to have either "definitive" NMO or NMOSD in the proportions listed in Table 15 below.

Table 15: Proportion of subjects with NMO or NMOSD in study 301, ITT

NMO Diagnosis	Eculizumab	Placebo	Subjects(filtered)
Definitive Neuromyelitis Optica	69 (71.9%)	38 (80.9%)	107 (50.2%)
NMO Spectrum Disorder	27 (28.1%)	9 (19.1%)	36 (16.9%)
Subjects(filtered)	96 (100.0%)	47 (100.0%)	213 (100.0%)

Source: JRev ADSL RANDFL_Y NMODxbyTRT01P.xls

Reviewer Comment: Because a positive test for anti-AQP4 antibodies was required to enter the trial, it is likely that all subjects in trial 301 would be considered to have definite NMO (NMOSD with AQP4 antibodies using the most recent terminology) by current standards which require only one core clinical characteristic and exclusion of alternative diagnoses if anti-AQP4 antibodies are present. There was no difference between these two diagnostic categories by baseline demographics or baseline disease characteristics. This may not be representative of differences between NMO and NMOSD in general

since in this study all subjects had to be positive for anti-AQP4 antibodies which are not required for a diagnosis of NMOSD.

Baseline Disability

The overall level of disability at baseline was moderate based on the median EDSS of 4, HAI of just over 2 and modified Rankin score of 2.

Table 16: EDSS, HAI, and mRS at baseline, ITT

Baseline assessment	Eculizumab	Placebo
EDSS		
Mean±SD	4.15±1.65	4.26±1.51
Range	1-7	1-6.5
Median	4	4
HAI		
Mean±SD	2.38±2.17	2.15±1.4
Range	0-8	0-6
Median	2	2
mRS		
Mean±SD	2.15±1.14	2.15±0.98
Range	0-4	0-4
Median	2	2

Source: RANDFL_Y Subset of ADSL BLMRS BLHAI BLEDSSbyTRT01PBy (TRT01P).jmp

The median number of previous relapses was 3 for both treatment groups.

Table 17: Number of historic relapses by treatment group, ITT

	Number of Historic Relapses (IEMHRELM)					
TRT01P	N	Mean	Std Dev	Min	Max	Median
Eculizumab	96	2.5	0.7	1	3	3
Placebo	47	2.4	0.8	1	3	3

Source: RANDFL_Y Subset of ADSL IEMHRELM By (TRT01P).jmp

The treatment groups were balanced for the proportion of subjects who had been treated with various individual ISTs (other than corticosteroids) prior to randomization (Table 18). The proportion of subjects who had not been treated with these drugs was 13.5% and 10.6% for the eculizumab and placebo groups respectively. These subjects were considered "treatment naïve".

Table 18: Prior Treatment with Immunosuppressant Therapies

Standardized Medication Name	Eculizumab	Placebo
Azathioprine	61 (63.5%)	26 (55.3%)
Rituximab	26 (27.1%)	20 (42.6%)
Mycophenolate Mofetil	27 (28.1%)	15 (31.9%)
Cyclophosphamide	9 (9.4%)	5 (10.6%)
Methotrexate	5 (5.2%)	5 (10.6%)
Glatiramer Acetate	7 (7.3%)	2 (4.3%)
Interferon Beta-1a	6 (6.3%)	3 (6.4%)
Interferon Beta-1b	3 (3.1%)	1 (2.1%)
Natalizumab	3 (3.1%)	1 (2.1%)
Interferon Beta	2 (1%)	1 (2.1%)
Ciclosporin	1 (1.0%)	2 (4.3%)
Fingolimod Hydrochloride	2 (2.1%)	1 (2.1%)
Mizoribine	1 (1.0%)	2 (4.3%)
Mitoxantrone	1 (1.0%)	2 (4.3%)
Mitoxantrone Hydrochloride	1 (1.0%)	1 (2.1%)
Tacrolimus Monohydrate	1 (1.0%)	1 (2.1%)
Tacrolimus	1 (1.0%)	1 (2.1%)
Tocilizumab	2 (2.1%)	0 (0.0%)
Bevacizumab	1 (1.0%)	0 (0.0%)
Interferon Alfa-2a	1 (1.0%)	0 (0.0%)
Cladribine	1 (1.0%)	0 (0.0%)
Leflunomide	1 (1.0%)	0 (0.0%)
Fingolimod	1 (1.0%)	0 (0.0%)
Subjects(filtered)	83 (86.5%)	42 (89.4%)
1stColItemSubjects	96 (100.0%)	47 (100.0%)

Source: JRevselADSLRANDFL_Y STDMEDNMbyADSLTRT01PfiltWHOLVL1_ANTINEO PRIOR_Yfiltcount.xls

Reviewer Comment: The proportion of subjects not on any IST at the time of randomization is higher than the treatment naïve proportions in the above table. This is presumably because of discontinuation of the "prior" ISTs by the time of randomization.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

At the time of randomization most subjects were continuing to be treated with one or more immunosuppressant drugs. Approximately 25% of each treatment group was not being treated with an IST during the blinded treatment phase. Azathioprine, with or without concurrent corticosteroids, was the most common concomitant IST used concurrently with the investigational drug (Table 19).

Reviewer Comment: The group not being treated with a concurrent immune therapy is larger than expected from pre-BLA discussions with the Division of

Neurology Products. This is an important subgroup to analyze both for efficacy and safety.

Table 19: IST use at randomization by treatment group, ITT

IST at randomization	Eculizumab		Placebo	
	n=96	%	n=47	%
corticosteroids alone	16	16.7%	11	23.4%
Azathioprine	37	38.5%	13	27.7%
Azathioprine alone	8	8.3%	6	12.8%
Azathioprine with corticosteroids	29	30.2%	7	14.9%
Mycophenolate mofetil	17	17.7%	8	17.0%
Mycophenolate mofetil alone	10	10.4%	5	10.6%
Mycophenolate mofetil with corticosteroids	7	7.3%	3	6.4%
Other ISTs	5	5.2%	2	4.3%
Other ISTs alone	1	1.0%	0	0.0%
Other ISTs plus corticosteroids	4	4.2%	2	4.3%
No IST use at randomization	21	21.9%	13	27.7%

Source: IST at RAND by TRT01P.xlsx

Concomitant Medications during the treatment phase are listed by WHO level 1 category in Table 20. The most commonly used nervous system medications were gabapentin (30-40% of subjects), carbamazepine (26%) and pregabalin (17-38%). The ten most common individual drugs are listed in

Table 20: Concomitant medications during the treatment phase, WHO level 1 category, randomized population

WHO DD ATC Text Level 1	Eculizumab	Placebo
Nervous System	86 (89.6%)	43 (91.5%)
Anti-infectives For Systemic Use	83 (86.5%)	38 (80.9%)
Alimentary Tract and Metabolism	79 (82.3%)	40 (85.1%)
Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins	69 (71.9%)	44 (93.6%)
Musculo-Skeletal System	65 (67.7%)	34 (72.3%)
Antineoplastic and Immunomodulating Agents	60 (62.5%)	23 (48.9%)
Respiratory System	52 (54.2%)	21 (44.7%)
Blood and Blood Forming Organs	46 (47.9%)	24 (51.1%)
Cardiovascular System	41 (42.7%)	19 (40.4%)
Genito Urinary System and Sex Hormones	35 (36.5%)	19 (40.4%)
Dermatologicals	30 (31.3%)	16 (34.0%)
Sensory Organs	25 (26.0%)	8 (17.0%)
Various	15 (15.6%)	10 (21.3%)
Subjects	96 (100.0%)	47 (100.0%)

Source: JRevAll ATCTX1byTRT01AfiltCONMEDFL_Y.xls

Table 21: Individual concomitant medications during the treatment phase, top ten, randomized population

Standardized Medication Name	Eculizumab	Placebo
Paracetamol	39 (40.6%)	21 (44.7%)
Azathioprine	37 (38.5%)	13 (27.7%)
Gabapentin	30 (31.3%)	19 (40.4%)
Prednisolone	31 (32.3%)	15 (31.9%)
Methylprednisolone	22 (22.9%)	20 (42.6%)
Baclofen	27 (28.1%)	14 (29.8%)
Carbamazepine	25 (26.0%)	13 (27.7%)
Pregabalin	16 (16.7%)	18 (38.3%)
Ciprofloxacin	19 (19.8%)	12 (25.5%)
Ibuprofen	17 (17.7%)	11 (23.4%)

Source: JRevALL STDMEDNMbyTRT01AfiltCONMEDFL_Y.xls

The antineoplastic and immune system medications being taken during treatment are of special interest and are listed in Table 22. The corticosteroids are listed in Table 23.

Table 22: Antineoplastic and immune system medications being taken during the treatment phase, randomized population

Standardized Medication Name	Eculizumab	Placebo
Azathioprine	37 (38.5%)	13 (27.7%)
Mycophenolate Mofetil	18 (18.8%)	8 (17.0%)
Cyclophosphamide	1 (1.0%)	1 (2.1%)
Methotrexate	1 (1.0%)	1 (2.1%)
Filgrastim	0 (0.0%)	1 (2.1%)
Ciclosporin	1 (1.0%)	0 (0.0%)
Tacrolimus Monohydrate	1 (1.0%)	0 (0.0%)
Mizoribine	1 (1.0%)	0 (0.0%)
Hochuekkito /07976001/	1 (1.0%)	0 (0.0%)
Subjects	96 (100.0%)	47 (100.0%)
1stCollItemSubjects	96 (100.0%)	47 (100.0%)

Source: JRevALL STDMEDNMbyTRT01AfiltCONMEDFL_Y ATCTXT1_ANTINEO.xls

Table 23: Corticosteroids and other drugs in the hormonal WHO 1 category being used during the treatment phase, randomized population

Standardized Medication Name	Eculizumab	Placebo
Prednisolone	31 (32.3%)	15 (31.9%)
Methylprednisolone	22 (22.9%)	20 (42.6%)
Prednisone	16 (16.7%)	5 (10.6%)
Methylprednisolone Sodium Succinate	6 (6.3%)	11 (23.4%)
Levothyroxine Sodium	8 (8.3%)	6 (12.8%)
Levothyroxine	5 (5.2%)	3 (6.4%)
Prednisolone Acetate	1 (1.0%)	3 (6.4%)
Dexamethasone	2 (2.1%)	2 (4.3%)
Hydrocortisone	2 (2.1%)	1 (2.1%)
Prednisolone Sodium Succinate	0 (0.0%)	2 (4.3%)
Dexamethasone Sodium Phosphate	2 (2.1%)	0 (0.0%)
Teriparatide	0 (0.0%)	1 (2.1%)
Tetracosactide	0 (0.0%)	1 (2.1%)
Methylprednisolone Acetate	0 (0.0%)	1 (2.1%)
Adrenal Cortical Extract	0 (0.0%)	1 (2.1%)
Fludrocortisone	0 (0.0%)	1 (2.1%)
Oxytocin	1 (1.0%)	0 (0.0%)
Meprednisone	1 (1.0%)	0 (0.0%)
Thyroid	1 (1.0%)	0 (0.0%)
Triamcinolone Acetonide	1 (1.0%)	0 (0.0%)
Liothyronine Sodium	1 (1.0%)	0 (0.0%)
Hydrocortisone Acetate	1 (1.0%)	0 (0.0%)
Glucagon	1 (1.0%)	0 (0.0%)
Fludrocortisone Acetate	1 (1.0%)	0 (0.0%)

Standardized Medication Name	Eculizumab	Placebo
Deflazacort	1 (1.0%)	0 (0.0%)
Carbimazole	1 (1.0%)	0 (0.0%)
Subjects	96 (100.0%)	47 (100.0%)

Source: JRevALL STDMEDNMbyTRT01AfiltCONMEDFL_Y ATCTX1_HORMONAL.xls

Efficacy Results – Primary Endpoint

The primary endpoint was the time to the first relapse as adjudicated by the Relapse Adjudication Committee. During the randomized treatment and post-treatment follow-up periods, the Treating Investigator evaluated 83 On-Trial Relapse Reports, 36 events in 34 subjects (35.4% of subjects) treated with eculizumab and 47 events in 33 subjects (70.2% of subjects) treated with placebo. The Treating Investigator (TI) made the determination that 15 of the 36 events in the eculizumab group and that 35 of the 47 events in the placebo group met the protocol definition of a relapse. The 15 events in the eculizumab group occurred in 14 subjects and the 35 events in the placebo group occurred in 29 subjects. Events determined by the TI to have met the protocol definition were referred to the Relapse Adjudication Committee (RAC) for final determination of whether an On-Trial Adjudicated Relapse had occurred. The RAC determined that 3 of the 15 events (20%) occurring in 3 subjects (21.4%) were Adjudicated On Trial Relapses and that 21 of the 35 events (60%) occurring in 20 subjects (72.4%) were adjudicated relapses. The disposition of the original 83 On Trial Relapse Reports is summarized in Table 24 below.

Table 24: Disposition of On Trial Relapses reports

Relapse Event Category	Eculizumab N = 96 Events/subjects	Placebo N = 47 Events/subjects
NMO Relapse On Trial Report	36/34	43*/33
% of subjects with an event	34/96 = 35.4%	33/47 = 70.2%
On Trial Relapse per Treating Investigator		
Events (no., % of On-Trial Reports)	15*/36 (41.7%)	31/43* (72%)
Subjects (no., % of subjects with an On-Trial report)	14/34 (41.2%)	29/33 (87.9%)
Adjudication of Investigator-determined relapses by RAC		
Events (no., % of Investigator determined relapses)	3/15** (20%)	21/31 (68%)
Subjects (no., % of subjects with an investigator determined relapse)	3/14 (21.4%)***	20/29 (72.4%)***
Overall rate of confirmation and adjudication		
Events (no., % of On-Trial Relapse reports)	3/36 (8.3%)	21/43 (48.8%)
Subjects (no., % of subjects with an On-Trial report)	3/34 (8.8%)	20/33 (60.6%)

*: There are 47 event terms but in 4 cases there are two terms reported for a single event, e.g. optic neuritis and myelitis. Therefore, there are 43 distinct events.
**: One of these events occurred outside of the window for relapses and was not included in the primary analysis – see sponsor response to AIR dated 04 April, 2019
***: primary endpoint

Reviewer Comment: The primary analysis of efficacy is dependent on the validity of the process of identifying relapses. The proportion of potential relapses that were determined to be protocol-defined relapses by the Treating Investigator for the placebo group was considerably higher compared to the eculizumab group. The same was true for those events referred to the RAC for adjudication. The unbalanced selection of events raises a concern for bias in the determination of which events represented valid relapses. A request for additional information was sent to the sponsor regarding this concern on March 28, 2019. The response on April 4, 2019, included a detailed disposition of potential relapses and a comment regarding the unbalanced selection of relapse events. Datasets were also requested that were intended to analyze the type and severity of the potential relapses.

There were 83 On Trial Relapse Reports, i.e. potential relapses reported to the investigator and assessed at a Relapse Evaluation Visit. The determination of the type of clinical event (CE database; CETERM) for these 83 reports is listed is Table 25 below.

Table 25: Determination by the Treating Investigator of the type of Clinical Event for On Trial Relapse Reports

	All events		Eculizumab		Placebo	
CETERM	n	% of events	n	% of events	n	% of events
Non-protocol defined relapse	33	39.8%	21	58.3%	12	25.5%
Protocol defined relapses	50	60.2%	15	41.7%	35	74.5%
Brain Stem	1	1.2%	0	0.0%	1	2.1%
Cerebral	1	1.2%	1	2.8%	0	0.0%
hoarse voice	1	1.2%	0	0.0%	1	2.1%
Optic Neuritis Bilateral	3	3.6%	1	2.8%	2	4.3%
Optic Neuritis Unilateral Left	8	9.6%	4	11.1%	4	8.5%
Optic Neuritis Unilateral Right	1	1.2%	1	2.8%	0	0.0%
Subtotal optic neuritis	12	24%	6	40%	6	17.1%
Pyramidal sign.	1	1.2%	0	0.0%	1	2.1%
Transverse Myelitis Complete	2	2.4%	1	2.8%	1	2.1%
Transverse Myelitis Complete Longitudinally extensive	1	1.2%	1	2.8%	0	0.0%
Transverse Myelitis Partial	19	22.9%	5	13.9%	14	29.8%
Transverse Myelitis Partial Longitudinally extensive	12	14.5%	1	2.8%	11	23.4%
Subtotal myelitis	35	70%	8	53.3%	27	77.1%
	83	100.0%	36	100.0%	47	100.0%

Source: CECAT_OTRreport Subset of EPOCH_OnTrial Subset of Join ADSLcCE TRT01P by (CETERM) 2.xlsx

The proportion of On Trial Relapse Reports determined by the TI to have met the protocol definition of a relapse that represented optic neuritis was higher in the eculizumab group (40% of events evaluated) compared to the placebo group (17%). Myelitis was more commonly determined to be the On Trial relapse in the placebo group ((77.1%) compared to the eculizumab group (53.3%).

> *Reviewer Comment: Events included in the primary analysis ultimately included only 3 events in the eculizumab group, 2 of which were optic neuritis, and 21 events in the placebo group, only 2 of which were optic neuritis.*

The change in neurologic deficit and disability was assessed to determine whether there was any indication of bias on the part of the TI in the determination of the severity of attacks required to meet the protocol definition. The sponsor was requested to provide datasets for both the On Trial Relapse reports and for the events adjudicated by the RAC with added

columns for the various measures of deficit and disability at the time of the 24 to 48 hour assessment of the potential relapse.

For those reports of a potential relapses assessed by the Treating Investigator, i.e. "On Trial Relapse Reports", assessment of EDSS, HAI, etc. was not required if it was determined that the event was a "non-protocol defined relapse". These assessments are therefore missing for 17 non-protocol defined relapses. They are also missing for 3 events that were protocol defined relapses, in 2 cases because the events were the second event for that subject and in one case because the event occurred beyond the allowable period after the end of treatment. For most of these non-protocol defined relapse events, little additional clinical information is available.

> *Reviewer Comment: In some of the subjects for whom the above assessments were missing, an adverse event was recorded that suggests minor neurologic symptoms such as minor sensory symptoms or non-specific weakness, or non-neurologic symptoms such as a "common cold" that may have resulted in a "pseudo-relapse".*

The Clinical Event terms recorded by the TI for those events for which there were clinical assessments are listed in Table 26 below.

Table 26: Clinical Event Term for On Trial Relapse reports for which clinical assessments were completed.

CETERM	Total	TRT01A	
	N Rows	N(Eculizumab)	N(Placebo)
Brain Stem	1	0	1
Cerebral	1	1	0
Hoarse voice	1	0	1
Non-protocol defined relapse	16	10	6
Optic Neuritis Bilateral	3	1	2
Optic Neuritis Unilateral Left	8	4	4
Optic Neuritis Unilateral Right	1	1	0
Pyramidal sign.	1	0	1
Transverse Myelitis Complete	2	1	1
Transverse Myelitis Complete Longitudinally extensive	1	1	0
Transverse Myelitis Partial	18	4	14
Transverse Myelitis Partial Longitudinally extensive	10	1	9

Source: EDSSEVAL not missing Subset of Join OTRreps from CEEVALplus c Rand_Y subset of ADSL TRT01A By (CETERM).jmp

For those events determined by the TI to be non-protocol defined relapses, the change in EDSS score within 24 to 48 hours of the event is shown in Table 27 below. There was a greater mean change in EDSS total score for events occurring in the placebo group.

Table 27: Change in EDSS from baseline to 24-48 hour relapse assessment, OTR reports, determined by TI to not meet the protocol definition of a relapse, assessments completed

	Change in EDSS from Baseline to 24-48 hours relapse evaluation (EDSSEVAL)						
TRT01P	N	Mean	Std Dev	Min	Max	Median	N Missing
Eculizumab	10	0.1	0.74	-0.5	2	0	0
Placebo	6	0.33	0.26	0	0.5	0.5	0

Source: Not RL Subset of EDSSEVAL not missing Subset of Join OTRreps from CEEVALplus c Rand_Y subset of ADSL CHG EDSSEVAL from BL By (TRT01P).jmp

Reviewer Comment: There is no indication for this subgroup of non-protocol defined relapses that the TI was biased toward selection of less severe events in the placebo group. The larger change in EDSS score at the time of a relapse in the placebo group does not necessarily indicate that attacks were more severe in the placebo group. The difference is most likely attributable to the predominance of events of myelitis in the placebo group and the relatively few such events in the eculizumab group.

For those 47 events that were determined to meet the protocol definition of a relapse, the change in EDSS score at the time of the event assessment was also greater for those in the placebo group (Table 28).

Table 28: Change in EDSS score from baseline for protocol defined relapses as determined by the TI

	Change in EDSS from Baseline to 24-48 hours relapse evaluation (EDSSEVAL)						
TRT01P	N Rows	Mean	Std Dev	Min	Max	Median	N Missing
Eculizumab	14	0.107	0.964	-1.5	2	0	0
Placebo	33	0.803	1.038	-1	3.5	0.5	0

Source: RL Subset of EDSSEVAL not missing Subset of Join OTRreps from CEEVALplus c Rand_Y subset of ADSL CHG EDSSEVALfromBL By (TRT01P).jmp

Reviewer Comment: As for those events determined to not meet the protocol definition of a relapse, the difference in the change in EDSS score at the time of the protocol-defined relapse may in part reflect the predominance of myelitis in the placebo group. As noted above, there is no indication of a bias in selecting less severe relapses in the placebo group.

The same pattern of larger differences in the change from baseline to the time of the relapse for those treated with placebo was seen for the EDSS ambulatory score, OSIS motor score, OSIS sensory score and HAI – for events determined to be non-protocol defined relapses and for those events determined by the TI to meet the protocol definition.

For those 45 events adjudicated by the RAC on referral from the TI, 21 events were adjudicated negatively. The mean change in EDSS score from baseline for these events was 0.182±1.031 (median 0) for the eculizumab group and 0.7±0.715 (median 0.75) for the placebo group.

For those 24 events that were adjudicated positively, the type of event is seen in Table 29. There is only one myelitis relapse in the eculizumab group and nearly all are myelitis in the placebo group.

Table 29: RAC adjudicated relapses by clinical event type

ADJUTYPE	N Rows	N(Eculizumab)	N(Placebo)
Area postrema attack	1	0	1
Myelitis	19	1	18
Optic Neuritis - Left Eye	2	0	2
Optic Neuritis - Left Eye / Optic Neuritis - Right Eye	1	1	0
Optic Neuritis - Right Eye	1	1	0

Source: ADJUSTATpositiveSubset of RLSETFL_Y Subset of ADRELAP plus 2 TRT01P By (ADJUTYPE).jmp

The change in EDSS score from baseline to the relapse evaluation is much greater for the placebo group, again most likely reflecting the predominance of myelitis in that treatment group (Table 30).

Table 30: Change in EDSS from baseline to Adjudicated On Trial Relapse

	Change in EDSS from baseline to potential relapse for those events adjudicated positive by the RAC							
TRT01P	N Rows	N	Mean	Std Dev	Min	Max	Median	N Missing
Eculizumab	3	3	-0.17	0.764	-1	0.5	0	0
Placebo	21	19	0.842	1.214	-1	3.5	0.5	2

Source: ADJUSTATpositiveSubset of RLSETFL_Y Subset of ADRELAP plus 2 BLEDSStoRL By (TRT01P).jmp

For the two optic neuritis attacks that occurred in each of the treatment groups, the change in visual function was not more severe in the placebo group (Table 31).

Table 31: Change in OSIS visual function score from baseline to Adjudicated On Trial Relapse

	Change in OSIS Visual Function from baseline to potential relapse for those events adjudicated positive by the RAC						
TRT01P	N Rows	Mean	Std Dev	Min	Max	Median	N Missing
Eculizumab	3	0.667	1.155	0	2	0	0
Placebo	21	0	1.414	-2	5	0	2

Source: ADJUSTATpositiveSubset of RLSETFL_Y Subset of ADRELAP plus 2 BLOSVAFtoRLBy (TRT01P).jmp

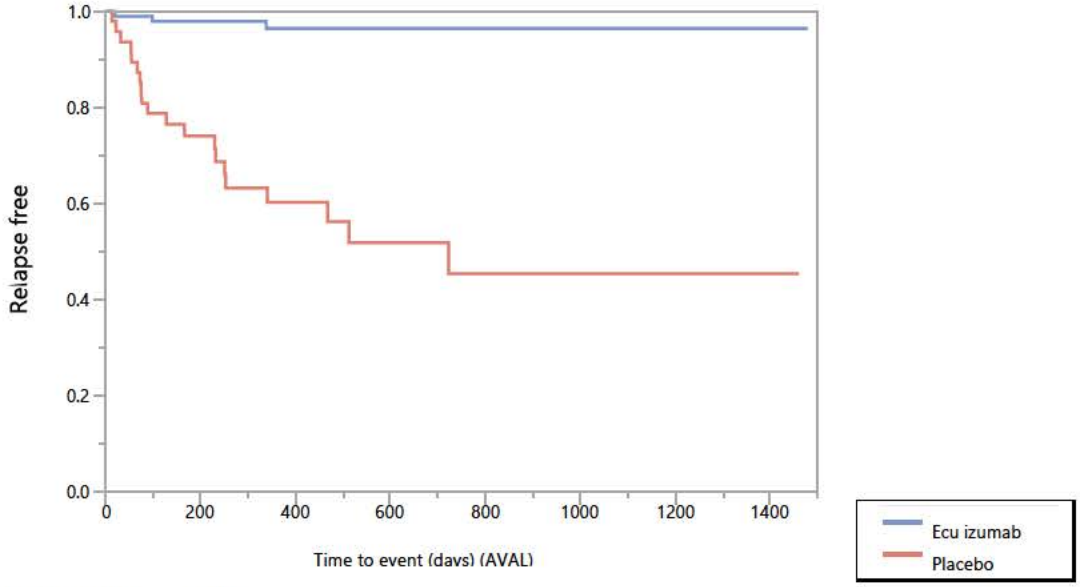
> ***Reviewer Comment: The disproportionate selection of potential relapse events from the placebo group, both by the TI and by the RAC, does raise a concern for biased selection. Furthermore, the RAC process was added to the protocol late in the conduct of the study when most of the potential relapses had already occurred. There is no indication that less severe events were being selected from the placebo group. There is no other indication of bias in the selection process. The analysis of the primary endpoint that includes all of the events selected by the TI is important in that it at least eliminates any bias introduced by the RAC process.***

Analysis of the primary endpoint

The Kaplan-Meier analysis of the time to the first Adjudicated On Trial Relapse is shown in **Figure 2**.

Figure 2: Time to the First RAC-adjudicated On-Trial Relapse, ITT

Product-Limit Survival Fit
Survival Plot



Time to event: AVAL
Censored by CNSR
Censor Code 1
Grouped by TRT01P of ADTTE

Summary

Group	Number failed	Number censored
Eculizumab	3	93
Placebo	20	27
Combined	23	120

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	41.3981	1	<.0001*

Source: RACRL1 subset of ADTTE, Survival Analysis (Reviewer analysis)

The treatment effect attributable to treatment with eculizumab is large and comparable to the analysis by the sponsor and by the Biometrics reviewer.

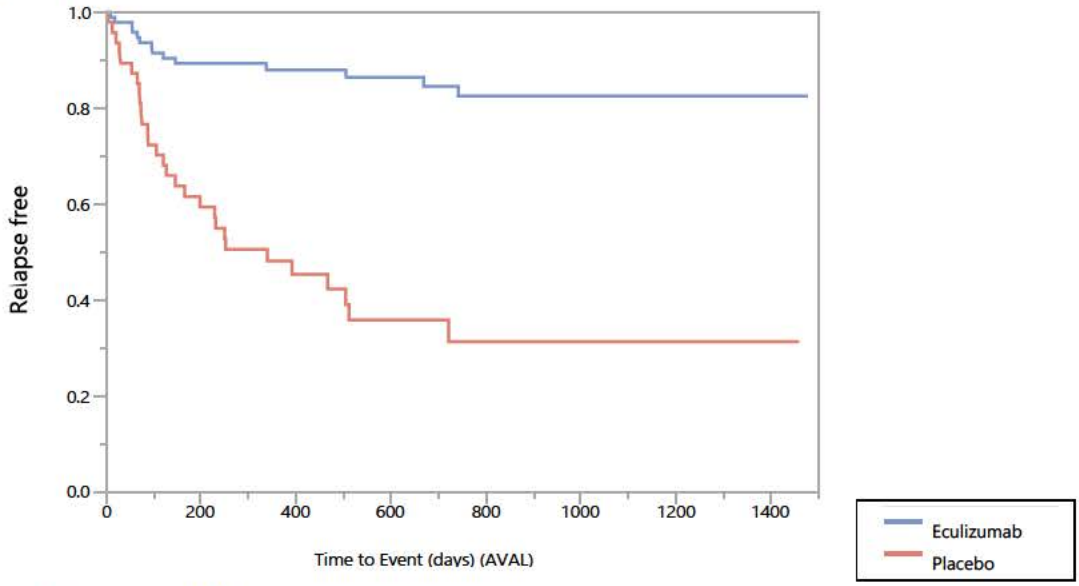
> *Reviewer Comment: As noted in earlier sections, nearly all of the events were myelitis in the placebo group and only one of three was myelitis in the eculizumab group.*

A key sensitivity analysis that includes all of the events determined to be On Trial Relapses by

the investigator regardless of the subsequent adjudication is shown in Figure 3.

Figure 3: Time to the first On Trial Relapse as determined by the TI

Product-Limit Survival Fit
Survival Plot



Time to event:	AVAL
Censored by	CNSR
Censor Code	1
Grouped by	TRT01P

Summary

Group	Number failed	Number censored
Eculizumab	14	82
Placebo	29	18
Combined	43	100

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	36.7905	1	<.0001*

Source: RLSET1 subset of ADTTE

Reviewer Comment: The statistically significant benefit when all relapses determined to meet the protocol criteria are included in the primary analysis is supportive of the primary endpoint analysis and is particularly important since the adjudication process was inserted very late into the trial and because of the apparent imbalance in the adjudication process.

The primary analysis of time to the first adjudicated On Trial Relapse by various demographic and disease characteristic subgroups did not reveal any significant differences in apparent efficacy. The risk ratio favors eculizumab in all subgroups.

Table 32: Primary endpoint analysis by demographic and baseline disease characteristic subgroups, ITT

	TRT01P	#events	#censored	Risk ratio	p-value*
Full FAS					
	Eculizumab	3	93	0.073	<0.0001
	Placebo	20	27		
By Sex					
Female	Eculizumab	3	85	0.089	<0.0001
	Placebo	16	26		
Male	Eculizumab	0	8	0.000	0.0032
	Placebo	4	1		
By Region					
Americas	Eculizumab	1	28	0.175	0.0657
	Placebo	3	12		
Asia-Pacific	Eculizumab	1	34	0.075	0.005
	Placebo	5	8		
Europe	Eculizumab	1	31	0.050	<0.0001
	Placebo	12	7		
By Age Group					
≤45	Eculizumab	0	47	0.000	<0.0001
	Placebo	14	10		
>45	Eculizumab	3	46	0.233	0.0123
	Placebo	6	17		
By Race					
Asian	Eculizumab	1	36	0.068	< 0.0002
	Placebo	6	9		
Black or African American	Eculizumab	0	9	0.000	0.1288
	Placebo	2	6		
White	Eculizumab	2	44	0.086	<0.0001
	Placebo	12	12		
By Medication Strata					
Changes in IST since last RL	Eculizumab	1	32	0.068	<0.0001
	Placebo	8	10		
Same IST since last RL	Eculizumab	2	47	0.098	<0.0001
	Placebo	10	14		
Treatment naive	Eculizumab	0	14	0.000	0.0085
	Placebo	2	3		

	TRT01P	#events	#censored	Risk ratio	p-value*
By EDSS stratum					
High EDSS (≥2.5 to ≤7)	Eculizumab	3	82	0.087	<0.0001
	Placebo	17	25		
Low EDSS (≤2.0)	Eculizumab	0	11	0.000	0.0037
	Placebo	3	2		

Source: ADTTE and RACRL1 Subset of Join ADTTE c ADSL.jmp
*: Log-Rank ; nominal p-value except for primary analysis

Reviewer Comment: Analysis of the primary endpoint by each subgroup is supportive of the overall result.

The primary analysis was also conducted by groupings of the concurrent immunosuppressant therapies allowed by protocol. Although the number of subjects in some subgroups is too small to draw statistical conclusions, the risk ratio favors eculizumab for each IST alone or in combination with corticosteroids (Table 33).

Table 33: Primary analysis by concurrent immunosuppressant therapy

By Concurrent IST					
	TRT01P	#events	#censored	Risk ratio	p-value*
Azathioprine any (no)	Eculizumab	1	58	0.039	<0.0001
	Placebo	15	19		
Azathioprine any (yes)	Eculizumab	2	35	0.140	0.013
	Placebo	5	8		
Azathioprine alone (no)	Eculizumab	3	85	0.082	<0.0001
	Placebo	17	24		
Azathioprine alone (yes)	Eculizumab	0	8	0.000	0.0103
	Placebo	3	6		
Azathioprine +corticosteroids (no)	Eculizumab	1	66	0.031	<0.001
	Placebo	18	22		
Azathioprine +corticosteroids (yes)	Eculizumab	2	27	0.241	0.0964
	Placebo	2	5		
Mycophenolate mofetil any (no)	Eculizumab	2	77	0.060	<0.0001
	Placebo	17	22		
Mycophenolate mofetil any (yes)	Eculizumab	1	16	0.167	0.0133
	Placebo	3	5		
Mycophenolate mofetil alone (no)	Eculizumab	2	84	0.054	<0.0001
	Placebo	18	24		
Mycophenolate mofetil alone (yes)	Eculizumab	1	9	0.25	0.2192
	Placebo	2	3		
MMF + corticosteroids no	Eculizumab	3	86	0.079	<0.0001
	Placebo	19	25		
MMF + corticosteroids yes	Eculizumab	0	7	0.000	0.1138
	Placebo	1	2		
Corticosteroids alone (no)	Eculizumab	3	77	0.085	<0.0001

By Concurrent IST					
	TRT01P	#events	#censored	Risk ratio	p-value*
	Placebo	16	20		
Corticosteroids alone (yes)	Eculizumab	0	16	0.000	0.0133
	Placebo	4	7		
No IST at baseline no	Eculizumab	3	72	0.105	<0.0001
	Placebo	13	21		
No IST at baseline yes	Eculizumab	0	21	0.000	<0.0001
	Placebo	7	6		
Historical use of rituximab no	Eculizumab	2	68	0.060	0.0001
	Placebo	13	14		
Historical use of rituximab yes	Eculizumab	1	25	0.156	0.0055
	Placebo	7	13		

Source: ADTTE and RACRL1 Subset of Join ADTTE c ADSL.jmp
*: Log-Rank; nominal p-value

Reviewer Comment: In early meetings with the sponsor, the Division indicated that the concurrent use of other ISTs could confound interpretation of the trial results. For each concurrent IST and IST combination, with or without corticosteroids, the primary analysis still favors therapy with eculizumab. Note that "treatment naïve" and "IST at baseline" are not the same.

Data Quality and Integrity

There were no concerns about the quality or integrity of the efficacy and safety data.

Efficacy Results – Secondary and other relevant endpoints

Annualized relapse Rate

The number of adjudicated on trial relapses was 3 in the eculizumab group and 21 in the placebo group. The period during which relapses may have been captured (STUPDUR) was 171.3 years for the eculizumab group and 52.41 years for the placebo group. The unadjusted ARR therefore was 0.0175 per year for the eculizumab group and 0.386 for the placebo group. This would represent a 95.5% reduction in the ARR.

Reviewer Comment: The study was not designed to assess the ARR because the period of observation was considerably shorter for those who had a relapse since these subjects entered the open-label extension following the first relapse. Because of the severity of NMOSD relapses, it was considered unethical to continue subjects on placebo following a single relapse. See the Biometrics review for further discussion of this endpoint.

Change in EDSS from BL

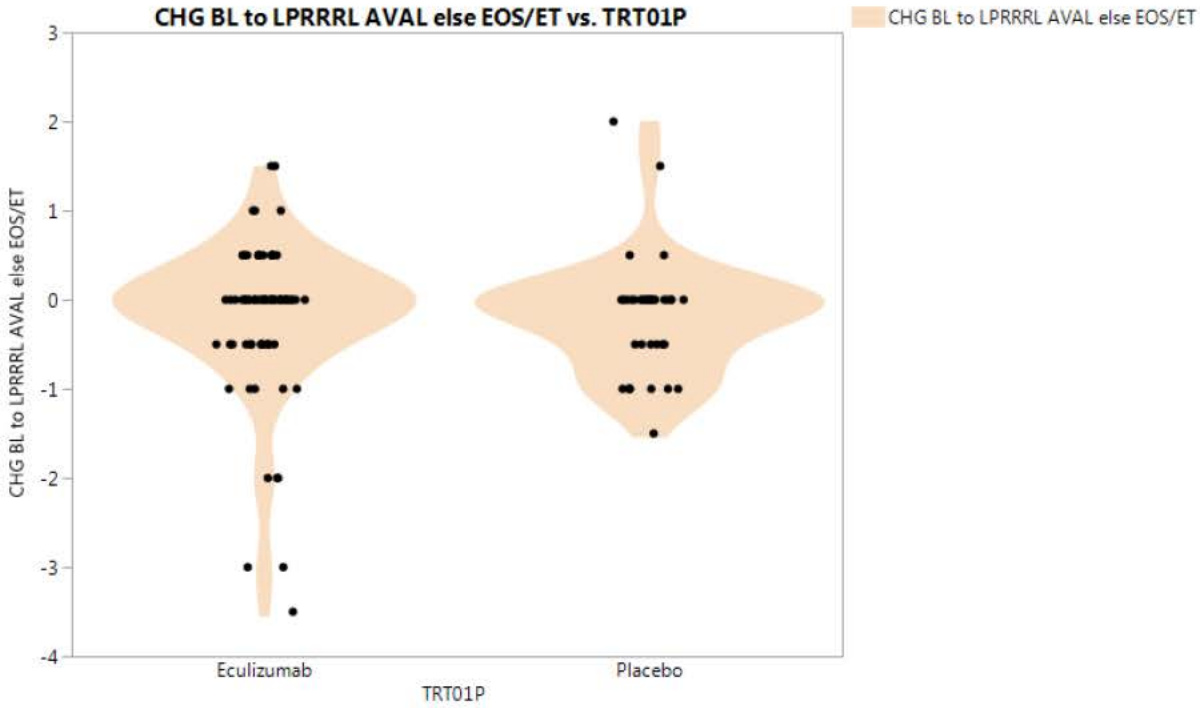
The period of observation for a change in EDSS score was considerably shorter for those who had a relapse and therefore shorter for the group treated with placebo. The study was not designed to assess for an effect on disability that would be independent of any effect on relapses. For this analysis this reviewer used the last EDSS score prior to the first relapse for those who had a relapse and the EDSS score at end of study for those who did not have a relapse. Not all subjects had an EDSS score done at these times. Table 34 below shows the change using the above values. There is no apparent difference in the change in EDSS score from baseline under those assumptions. The distribution of the changes is seen in Figure 4.

Table 34: Change in EDSS score from baseline to prior to first relapse or to end of study, randomized population

	CHG BL to LPRRRL AVAL else EOS/ET						
TRT01P	**N**	**Mean**	**Std Dev**	**Min**	**Max**	**Median**	**N Missing**
Eculizumab	78	-0.19	0.869	-3.5	1.5	0	18
Placebo	38	-0.18	0.662	-1.5	2	0	9

Source: LPRRRLFL_Y Subset of PARAM_EDSS Subset of ADEDSS CHG BL to LPRRRLelseEOSETBy (TRT01P).jmp

Figure 4: Distribution of the change in EDSS from baseline to prior to first relapse or end of study



Another way of assessing the change in EDSS score would be to assess the change in baseline EDSS score from Study 301 to Study 302 for those subjects included in the Study 302 database at the time of submission. Table 35 shows that change for those who did and did not have an adjudicated on-trial relapse in Study 301, by treatment group.

Table 35: Change in baseline EDSS score from Study 301 to Study 302, with and without an adjudicated on-trial relapse in period 1, Study 302 population

		CHG EDSS 302BL from 301BL					
RACR01FL of 301	TRT01P of 301	N	Mean	Std Dev	Min	Max	Median
N	Eculizumab	11	0	0.78	-1	2	0
N	Placebo	7	-0.143	0.63	-1.5	0.5	0
Y	Eculizumab	3	-0.333*	0.58	-1	0	0
Y	Placebo	18	0.361*	1.25	-2	3	0

Source: CHG 301BL to 301BL Join 301BLand302BL EDSSsubset of ADEDSS302 By RACR01FLandTRT01P.jmp
*: p=0.3643, unpaired t-test

Reviewer Comment: The median change for those with and those without a relapse, for both treatment groups, was zero. The mean differences are not statistically significant. The difference is likely due to the fact that only one of the three adjudicated OTRs in the eculizumab group was an attack of myelitis whereas nearly all were myelitis in the placebo group. Conclusions regarding an effect on disability are limited by the small number of subjects, the short period of observation and a termination of observations after one relapse. (b) (4).

Change in modified Rankin Scale score from baseline

The same issues noted for the other secondary endpoints apply to the change in modified Rankin Scale (mRS). Using the same methods as for this reviewer's analysis of the change in EDSS score, the change in mRS from baseline is shown in Table 36.

Table 36: Change in mRS from baseline to prior to first relapse or end of study, randomized population

	CHG BL to LPRRRL else to EOS						
TRT01P	N	Mean	Std Dev	Min	Max	Median	N Missing
Eculizumab	96	-0.25	0.711	-4	2	0	0
Placebo	47	-0.09	0.583	-2	2	0	0

Source: LPRRRLFL_Y Subset of RACRELFL_Y Subset of mRS Subset of ADEFF CHG BLtoLPRRRLelseEOSBy (TRT01P).jmp

Reviewer Comment: The median change was zero. See the Biometrics review for a discussion of the statistical significance of this endpoint. The result is nominal since the endpoint earlier in the hierarchy was not significant.

Change in HAI score from baseline

The study design limits analysis of the change in HAI for the same reasons as for the EDSS and the mRS. For the group with a baseline HAI for the start of study 302, there was no significant change in the HAI (Table 37).

Table 37: Change in baseline HAI score from Study 301 to Study 302, with and without an adjudicated on-trial relapse in period 1, Study 302 population

		CHG HAI BL1 to BL2			
RACR01FL	TRT01P	N Rows	Mean	Std Dev	Median
N	Eculizumab	11	-0.2	0.4	0
N	Placebo	7	0.43	0.79	0

RACR01FL	TRT01P	CHG HAI BL1 to BL2			
		N Rows	Mean	Std Dev	Median
Y	Eculizumab	3	-0.7	2.52	-1
Y	Placebo	18	1.06	2.39	0

Source: ADSL 302 By CHG HAI BL1toBL2 (RACR01FL, TRT01P).jmp

Change in EQ-5D VAS

The change in EQ5DVAS from baseline to end of study for the all randomized subjects is listed in Table 38. As for the other secondary endpoints, the significance of any difference is unclear since follow-up was not uniform for all subjects.

Table 38: Change in EQ5DVAS from baseline to EOS, randomized population

TRT01P	Change EQ5DVAS from Baseline to EOS			
	N	Mean	Std Dev	Median
Eculizumab	96	5.42	18.5	0
Placebo	47	0.57	16.4	0

Source: AVISIT_EOS Subset of VAS Subset of ADEQ5D CHG from BL By (TRT01P).jmp

Dose/Dose Response

A single dose was studied.

Durability of Response

The durability of the measures of efficacy was not studied.

Persistence of Effect

The persistence of efficacy was not studied.

Additional Analyses Conducted on the Individual Trial

There are no relevant additional analyses other than those described in the above sections.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Efficacy is based on a single adequate and well-controlled trial. Therefore, an ISE/SCE is not applicable. The sponsor provides a comparison of the ARR from the open-label safety extension in to the ARR in the 24 months prior to the controlled study. This is not considered a valid comparison because the number of prior relapses was not collected prospectively, the number of relapses may decrease over time for both groups and there was no concurrent comparator in the open label phase of the study.

7.1.1. Primary Endpoints – N/A

7.1.2. Secondary and Other Endpoints – N/A

7.1.3. Subpopulations – N/A

7.1.4. Dose and Dose-Response – N/A

7.1.5. Onset, Duration, and Durability of Efficacy Effects – N/A

7.2. Additional Efficacy Considerations - none

7.2.1. Considerations on Benefit in the Postmarket Setting - N/A

7.2.2. Other Relevant Benefits - N/A

7.3. Integrated Assessment of Effectiveness - N/A

8. Review of Safety

8.1. Safety Review Approach

The assessment of safety is based primarily on the safety results of the single controlled clinical trial 301 where there was a placebo comparator. Additional safety data are available for those subjects who were treated with eculizumab in the uncontrolled extension study 302. The safety of eculizumab for other indications can serve as a reference for the results seen in the studies of NMOSD.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety database is composed of the 96 patients treated with eculizumab and the 47 patients treated with placebo during the controlled phase of Study 301. 14 of the 14 patients treated with eculizumab and 25 of the 29 treated with placebo, who experienced an On Trial Relapse as determined by the investigator, continued in the open label extension study and continued to be treated or were initiated on treatment with eculizumab. This was done in a blinded procedure to maintain the blind until Study 301 was completed. There were additional subjects who were treated in Study 301 and who did not have an On Trial Relapse event. These subjects may also have been eligible for the open label extension study if they completed the study ECU-NMO-301 study, i.e., completed either Week 6 Follow-up Relapse Evaluation Visit or End of Study Visit. These subjects were not included as treated with eculizumab in the original submission, but these subjects were included in the 90-day safety update. As of the safety update, the total number of subjects treated with any dose of eculizumab in Study 302 is 137, 96 who had been treated with eculizumab in Study 301 and 41 treated with placebo in Study 301. The total exposure for the controlled phase of Study 301 and for all subjects treated with eculizumab is shown in Table 39.

Table 39: Eculizumab exposure for Study 301 and all exposure, safety population

	ECU-NMO-301		All eculizumab
	Placebo	Eculizumab	Eculizumab
Number of subjects	N = 47	N = 96	N = 137*
Study duration (days)			
Mean±1SD	407.3±357	651.8±394	744.6±443.8
Median	302	626	703
Subject years	52.4	171.3	279.3
Treatment duration (days)			
Mean±1SD	400.6±360	646.9±396	737.4±444.8
Median	289	626	693
Subject years	51.6	170	275.46
Total exposure (mg)			
Mean±1SD	-	56927±33434	64782±37835
Maximum	-	127200	145200
Minimum	-	3600	900
Median	-	55200	62400

Reviewer calculations
*: 6 subjects never treated with eculizumab excluded

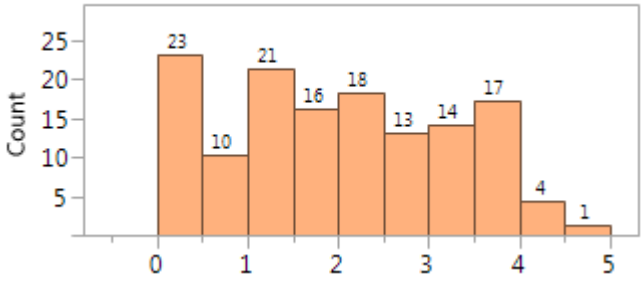
8.2.2. Relevant characteristics of the safety population:

The demographics and baseline disease characteristics of the safety population are essentially the same as those listed in Section 6.1.2 because they are the same subjects who were treated initially in Study 301.

8.2.3. Adequacy of the safety database:

The controlled safety database for NMOSD is limited to the 96 subjects treated in Study 301; 78 of this group continued treatment in the open label extension Study 302. The safety database also includes the 41 subjects treated with placebo in study 301 who initiated treatment with eculizumab in Study 302. For study 301 there are 67 subjects with a treatment duration of one year or more. At the time of the safety update there were 104 subjects who were treated with eculizumab for NMOSD for one year or more. The distribution of treatment duration is shown in **Figure 5**.

Figure 5: All eculizumab treatment duration, years, safety population



In addition, there is extensive safety data from the use of eculizumab for the approved indications. The original submission for Generalized Myasthenia Gravis (S422) included 133 patients exposed to eculizumab, 62 in a placebo-controlled trial. One-hundred ninety-six (196) trial subjects with Paroxysmal Nocturnal Hemoglobinuria were exposed to eculizumab, 182 for more than one year. Seventy-eight (78) patients with Atypical Hemolytic Uremic Syndrome were treated with eculizumab in single-arm studies with a median treatment duration of 67 weeks. There is an extensive database of post-marketing reports available as well.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no issues regarding the integrity or quality of the safety data submitted.

8.3.2. Categorization of Adverse Events

Adverse events were categorized using standard MedDRA terminology. Verbatim terms were converted to preferred terms using MedDRA dictionary version 21.0. Adverse events of special interest were: meningococcal infections, Aspergilla infections, other serious infections, sepsis, infusion reactions, serious cutaneous allergic reactions, cardiac disorders, and angioedema. In general, coding and grouping of adverse events were acceptable and allowed an accurate assessment of safety. An additional assessment of safety was conducted by this reviewer using

the ODE1 adverse event groupings.

8.3.3. Routine Clinical Tests

The timing of the clinical tests that were performed and the specific laboratory studies that were collected are shown in detail in Appendix **13.7**. These assessments allowed an adequate assessment of vital signs, ECG and routine hematology and chemistry.

8.4. Safety Results

8.4.1. Deaths

There was one death in Study 301 and none in Study 302. This subject (b) (6) was a 30-year old black male with an extensive history of respiratory illnesses including asthma, bronchiectasis, chronic obstructive pulmonary disease, pulmonary fibrosis, and residual tracheal stenosis due to a previous tracheostomy. He had pneumonia on two previous occasions. He was morbidly obese and had a history of sleep apnea and was a chronic tobacco user. Concomitant medications were azathioprine, oxycodone, tramadol, temazepam and supplemental vitamin D. He was diagnosed with NMOSD at the age of 25 years. He received the first dose of study drug (eculizumab, 900 mg IV) on (b) (6). At an infusion visit on study day 759 he began to develop shortness of breath and difficulty walking. The infusion scheduled for study day 774 was not done and the subject was hospitalized. Admission diagnoses included congestive heart failure, pneumonia, pulmonary empyema, and sepsis. Total white blood cell count was elevated at 18.2 X 103/µL. He was started on vancomycin, piperacillin/tazobactam. Computerized tomography scan showed no pulmonary embolus, a small right sided and moderately large left pleural effusion, right lower lobe consolidation with centrilobular emphysematous change, pulmonary artery dilatation with right ventricular dilatation, mediastinal lymphadenopathy, and hepatosplenomegaly. A chest X-ray showed opacification of left lung base and some opacity in the right lung base. He underwent a left thoracotomy with total pulmonary decortication. Surgical culture from the left pleural fluid showed 4+ Streptococcus intermedius susceptible to penicillin, ceftriaxone, and vancomycin. Subsequently, anaerobic culture of the left pleural fluid obtained on (b) (6) (b) (6) (Study Day 760) also grew Peptostreptococcus micros. On (b) (6) (Study Day 776), laboratory test results showed brain natriuretic peptide 3926 pg/mL (reference range 0 to 450 pg/mL). On (b) (6) [Study Day 777]), the patient developed progressive hypotension requiring vasopressor support and subsequently died due to the serious event of infectious pleural effusion.

Reviewer Comment: Although treatment with eculizumab may have increased this subject's susceptibility to infection, the underlying serious pulmonary disease appears to have been the primary cause of this event.

Subject [redacted] died just after being withdrawn from the study. This subject was a 63-year old woman with a previous history of hypertension, tobacco use, COPD, a malignant lung neoplasm, blindness, and hyperglycemia. The first dose of eculizumab was given on [redacted] Prednisolone was a relevant concomitant medication. Ciprofloxacin was being given for meningococcal prophylaxis. There were subsequent AEs of exacerbation of airway disease [redacted] pneumococcal infection [redacted] pneumonia, pulmonary embolism and pancreatitis [redacted]. Study drug was discontinued due to adverse events in [redacted]. In [redacted] SAEs of pneumonia and myocardial ischemia resulted in hospitalization. On [redacted] "while the patient was off study", the patient died. The final cause of death was pneumonia with a secondary diagnosis of myocardial ischaemia.

Reviewer Comment: The subject died within about 2 months of the last dose of eculizumab and had a history of recurrent pneumonias and other respiratory AEs since starting treatment. Treatment with eculizumab may have played a role in this fatal outcome.

8.4.2. Serious Adverse Events

In the controlled Study 301, 55 SAEs occurred in 30 subjects treated with eculizumab (31.3%) and 47 SAEs occurred in 26 subjects (55.3%) in the placebo group. Based on the time of study observation, the incidence of SAEs in the group treated with eculizumab was 32.1 per 100 subject-years and 89.7 per 100 subject-years in the placebo group. Approximately 15% of SAEs occurred during the induction phase, 75-85% during the maintenance phase and 15-20% during the post-treatment follow-up phase. The most common SAEs are in Table 40 below. Excluding NMOSD relapses, an approximately equal number of subjects in the eculizumab group (26.0%) and the placebo group (27.7%) had an SAE.

Table 40: Serious adverse events by actual treatment, Study 301, occurring in 2 or more subjects in either treatment group.

Dictionary Derived Term	Eculizumab (N=96)		Placebo (N=47)		Total Subjects (N=143)	
	n	%	n	%	n	%
Neuromyelitis optica spectrum disorder	7	7.3%	16	34.0%	23	16.1%
Pneumonia	3	3.1%	1	2.1%	4	2.8%
Cellulitis	2	2.1%	0	0.0%	2	1.4%
Sepsis	2	2.1%	0	0.0%	2	1.4%
Urinary tract infection	2	2.1%	0	0.0%	2	1.4%

Source: JRevADSL SAFFL_Y AEDECODbyTRT01AfilterAESER_YandTRTEMFL_Y sorted.xls

For both treatment groups, excluding relapses, the most common SAEs were in the Infections and Infestations SOC (Table 41) below.

Table 41: Serious adverse events by SOC in study 301, safety population

Body System or Organ Class	Eculizumab	Placebo	Subjects
Nervous system disorders	7 (7.3%)	19 (40.4%)	26 (18.2%)
Infections and infestations	11 (11.5%)	6 (12.8%)	17 (11.9%)
Injury, poisoning and procedural complications	4 (4.2%)	1 (2.1%)	5 (3.5%)
Gastrointestinal disorders	3 (3.1%)	2 (4.3%)	5 (3.5%)
Respiratory, thoracic and mediastinal disorders	3 (3.1%)	2 (4.3%)	5 (3.5%)
Eye disorders	3 (3.1%)	0 (0.0%)	3 (2.1%)
Cardiac disorders	2 (2.1%)	1 (2.1%)	3 (2.1%)
Musculoskeletal and connective tissue disorders	2 (2.1%)	1 (2.1%)	3 (2.1%)
Blood and lymphatic system disorders	1 (1.0%)	2 (4.3%)	3 (2.1%)
Vascular disorders	2 (2.1%)	1 (2.1%)	3 (2.1%)
Hepatobiliary disorders	1 (1.0%)	1 (2.1%)	2 (1.4%)
General disorders and administration site conditions	2 (2.1%)	0 (0.0%)	2 (1.4%)
Psychiatric disorders	0 (0.0%)	2 (4.3%)	2 (1.4%)
Ear and labyrinth disorders	0 (0.0%)	1 (2.1%)	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	1 (2.1%)	1 (0.7%)
Surgical and medical procedures	1 (1.0%)	0 (0.0%)	1 (0.7%)
Renal and urinary disorders	1 (1.0%)	0 (0.0%)	1 (0.7%)
Subjects	96 (100.0%)	47 (100.0%)	143 (100.0%)
Demominator	Column total	Column total	(ActiveSubset)

Source: JRevselADSL RANDFL_Y SOCbyTRT01AfiltAESER_Y TRTEMFL_Y.xls; JRevselADSL RANDFL_Y SOCbyTRT01AfiltAESER_Y TRTEMFL_Ycoltot.xls

No single serious infection was prominent in either treatment group (Table 42).

Table 42: SAEs in the Infections and Infestations SOC, safety population

Dictionary Derived Term	Eculizumab	Placebo
Appendicitis	1 (1.0%)	0 (0.0%)
Bartholin's abscess	1 (1.0%)	0 (0.0%)
Bronchitis	1 (1.0%)	1 (2.1%)
Cellulitis	2 (2.1%)	0 (0.0%)
Gallbladder empyema	1 (1.0%)	0 (0.0%)
Gastroenteritis viral	0 (0.0%)	1 (2.1%)
Herpes zoster	0 (0.0%)	1 (2.1%)
Infectious pleural effusion	1 (1.0%)	0 (0.0%)
Influenza	1 (1.0%)	1 (2.1%)
Pneumococcal infection	0 (0.0%)	1 (2.1%)

Dictionary Derived Term	Eculizumab	Placebo
Pneumonia	3 (3.1%)	1 (2.1%)
Renal abscess	1 (1.0%)	0 (0.0%)
Sepsis	2 (2.1%)	0 (0.0%)
Septic shock	0 (0.0%)	0 (0.0%)
Urinary tract infection	3 (3.1%)	0 (0.0%)
Viral upper respiratory tract infection	0 (0.0%)	1 (2.1%)
Total Subjects	96 (100.0%)	47 (100.0%)
		(Denom=ColTot)

Source: JRevAEDECODbyTRT01AofADSLfilterAESER_YandSOC_INFINF.xls

There were no infections with Neisseria species or Aspergilla during study 301. There were 2 cases of sepsis, both in the eculizumab group and starting on days 860 and 774. One subject recovered, and the other event was fatal. See 8.4.1 for the narrative for the latter subject. One subject had a fatal outcome following recurrent pneumonias and other respiratory adverse events. The death occurred two months after eculizumab was discontinued for a previous episode of pneumonia and a few days after formally being withdrawn from the study. The death is not included in the sponsor's formal analyses because the subject was off study at the time of death. Nevertheless, eculizumab treatment may have contributed to the outcome. The narrative for this subject is in Section 8.4.1.

Herpes infections

There 12 events of a Herpes virus infection in 7 subjects in the eculizumab group and 3 events in 3 subjects in the placebo group. None of the events in the eculizumab group was considered serious. All were oral or genital herpes infection with the exception of one case of herpes zoster. One event of herpes zoster in the placebo group (ECU-NMO-301-(b) (6) was considered serious. The subject presented on study day 286 with fever and chills and flank pain. She was hospitalized with Herpes zoster in the T8 dermatome which resolved. She was discharged on study day 291. The other two herpes infections in the placebo group were oral or genital herpes simplex infections.

The incidence of SAEs was not higher in the eculizumab group when eculizumab was combined with either the same or changed IST therapy, or in treatment naïve subjects, compared to the placebo group in the same IST category at baseline (Table 43).

Table 43: SAEs by baseline IST stratification, safety population

IST Observed Stratification	Eculizumab	Placebo	Subjects
Changes in IST(s) Since Last Relapse at Randomization	12 (13.6%)	10 (22.2%)	22 (10.3%)

IST Observed Stratification	Eculizumab	Placebo	Subjects
Continuing on Same IST(s) Since Last Relapse at Randomization	16 (18.2%)	12 (26.7%)	28 (13.1%)
Treatment Naive at Randomization	2 (2.3%)	4 (8.9%)	6 (2.8%)
Subjects	88 (100.0%)	45 (100.0%)	213 (100.0%)

Source: JRevADSL SAFFL_Y ISTOBSSTRATbyTRT01AfiltADAESER_Y.xls

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

An AE resulted in discontinuation of study drug in 3 subjects, all in the placebo group. The three events were pneumonia on day 159, pre-renal failure on study day 369 and pancytopenia on study day 369.

An AE resulted in interruption of the study drug for 55 AEs, 43 events in 20 subjects in the eculizumab group and for 12 events 6 subjects in the placebo group. Two of these were IRRs in the eculizumab group (none in the placebo group). Overall, no single AE event was of concern.

8.4.4. Significant Adverse Events

There were 1300 adverse events, serious and non-serious, occurring in 88 subjects in the group treated with eculizumab and 617 events in 45 subjects treated with placebo. The overall incidence of adverse events per subject-year was 7.65 for the eculizumab group and 11.97 for the placebo group.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Adverse events by study period are listed in Table 44 below.

Table 44: Adverse events by study period

Epoch	Eculizumab	Placebo	Subjects(filtered)
(missing)	1 (1.1%)	2 (4.4%)	3 (1.4%)
DOUBLE-BLIND TREATMENT INDUCTION	58 (65.9%)	22 (48.9%)	80 (37.6%)
DOUBLE-BLIND TREATMENT MAINTENANCE	80 (90.9%)	43 (95.6%)	123 (57.7%)
POST TREATMENT	16 (18.2%)	11 (24.4%)	27 (12.7%)
Subjects(filtered)	88 (100.0%)	45 (100.0%)	213 (100.0%)
			(Denom=ColTot)

Source: JRevADAE EPOCHbyTRT01AfilterTRTEMFL_Y.xls

The adverse events and serious adverse events that occurred during the 4-week induction phase when doses were given weekly do not appear to differ from those that occurred during

the much longer maintenance phase. There were two infusion related reactions in the eculizumab group during the induction phase, neither of which was serious.

For the overall study, adverse events that occurred in 10% of more of subjects are listed in Table 45. Those that occurred more often in the eculizumab group are shaded.

Table 45: Adverse events that occurred in 10% of more of the study 301 safety population treated with eculizumab.

Dictionary Derived Term	Eculizumab	Placebo
Upper respiratory tract infection	28 (29.2%)	6 (12.8%)
Headache	22 (22.9%)	11 (23.4%)
Nasopharyngitis	20 (20.8%)	9 (19.1%)
Nausea	16 (16.7%)	12 (25.5%)
Diarrhoea	15 (15.6%)	7 (14.9%)
Back pain	15 (15.6%)	6 (12.8%)
Dizziness	14 (14.6%)	6 (12.8%)
Urinary tract infection	13 (13.5%)	10 (21.3%)
Pain in extremity	11 (11.5%)	10 (21.3%)
Cough	11 (11.5%)	7 (14.9%)
Arthralgia	11 (11.5%)	5 (10.6%)
Influenza	11 (11.5%)	2 (4.3%)
Vomiting	10 (10.4%)	8 (17.0%)
Pharyngitis	10 (10.4%)	3 (6.4%)
Contusion	10 (10.4%)	2 (4.3%)
Subjects(filtered)	96 (100.0%)	47 (100.0%)

Source: JRev301 AEDECODbyTRT01AfilterSAFFL_Y.xls

The most common adverse events overall were in the SOC of Infections and Infestations (Table 46). These were slightly more common in the eculizumab group. AEs in the Blood and Lymphatic disorders SOC were about twice as common in the eculizumab group.

Table 46: Adverse events by SOC, study 301, safety population.

Body System or Organ Class	Eculizumab	Placebo
Infections and infestations	73 (76.0%)	32 (68.1%)
Nervous system disorders	46 (47.9%)	32 (68.1%)
Gastrointestinal disorders	44 (45.8%)	26 (55.3%)
Musculoskeletal and connective tissue disorders	44 (45.8%)	23 (48.9%)
Injury, poisoning and procedural complications	32 (33.3%)	19 (40.4%)
General disorders and administration site conditions	28 (29.2%)	18 (38.3%)
Skin and subcutaneous tissue disorders	27 (28.1%)	18 (38.3%)
Respiratory, thoracic and mediastinal disorders	24 (25.0%)	17 (36.2%)
Eye disorders	22 (22.9%)	9 (19.1%)

Body System or Organ Class	Eculizumab	Placebo
Investigations	16 (16.7%)	14 (29.8%)
Renal and urinary disorders	18 (18.8%)	8 (17.0%)
Blood and lymphatic system disorders	21 (21.9%)	5 (10.6%)
Psychiatric disorders	14 (14.6%)	11 (23.4%)
Metabolism and nutrition disorders	14 (14.6%)	9 (9.1%)
Vascular disorders	13 (13.5%)	8 (17.0%)
Reproductive system and breast disorders	10 (10.4%)	8 (17.0%)
Ear and labyrinth disorders	7 (7.3%)	5 (10.6%)
Cardiac disorders	5 (5.2%)	4 (8.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (5.2%)	3 (6.4%)
Hepatobiliary disorders	4 (4.2%)	3 (6.4%)
Immune system disorders	3 (3.1%)	3 (6.4%)
Endocrine disorders	4 (4.2%)	0 (0.0%)
Social circumstances	0 (0.0%)	1 (2.1%)
Surgical and medical procedures	1 (1.0%)	0 (0.0%)
Subjects(filtered)	96 (100.0%)	47 (100.0%)

Source: JRev301AE SOCbyTRT01AfilterSAFFL_Y.xls

The specific AE infection terms are listed in Table 47. Upper respiratory tract infections were considerably more common in the eculizumab group. Opportunistic infections such as Candida infections were not more common in the eculizumab group.

> *Reviewer Comment: The majority of subjects in this trial were on other immunosuppressant drugs concurrently. This may have enhanced the risk of infection in those subjects.*

Table 47: AE terms in the Infections and Infestations SOC, study 301, safety population

Dictionary Derived Term	Eculizumab	Placebo
Upper respiratory tract infection	28 (38.4%)	6 (18.8%)
Nasopharyngitis	20 (27.4%)	9 (28.1%)
Urinary tract infection	13 (17.8%)	10 (31.3%)
Conjunctivitis	9 (12.3%)	4 (12.5%)
Pharyngitis	10 (13.7%)	3 (9.4%)
Influenza	11 (15.1%)	2 (6.3%)
Bronchitis	9 (12.3%)	3 (9.4%)
Cystitis	8 (11.0%)	1 (3.1%)
Pneumonia	3 (4.1%)	4 (12.5%)
Hordeolum	7 (9.6%)	0 (0.0%)
Sinusitis	6 (8.2%)	0 (0.0%)
Oral herpes	4 (5.5%)	2 (6.3%)

Dictionary Derived Term	Eculizumab	Placebo
Cellulitis	5 (6.8%)	1 (3.1%)
Oral candidiasis	0 (0.0%)	2 (6.3%)
Oesophageal candidiasis	1 (1.4%)	1 (3.1%)
Vulvovaginal candidiasis	2 (2.7%)	0 (0.0%)
Pneumococcal infection	0 (0.0%)	1 (3.1%)
Pneumonia klebsiella	0 (0.0%)	1 (3.1%)

Source: JRev301AEDECODbyTRT01AfilterSAFFL_YandSOC_INFINF.xls

The adverse events for the Blood and Lymphatics Disorders SOC are listed in Table 48.

Table 48: AEs for the Blood and Lymphatics Disorders SOC, Study 301, safety population

Dictionary Derived Term	Eculizumab	Placebo	Subjects
Leukopenia	5 (5.2%)	1 (2.1%)	6 (4.2%)
Lymphopenia	5 (5.2%)	0 (0.0%)	5 (3.5%)
Iron deficiency anaemia	3 (3.1%)	1 (2.1%)	4 (2.8%)
Lymphadenopathy	3 (3.1%)	1 (2.1%)	4 (2.8%)
Anaemia	2 (2.1%)	1 (2.1%)	3 (2.1%)
Neutropenia	3 (3.1%)	0 (0.0%)	3 (2.1%)
Thrombocytopenia	1 (1.0%)	1 (2.1%)	2 (1.4%)
Eosinophilia	1 (1.0%)	0 (0.0%)	1 (0.7%)
Anaemia macrocytic	1 (1.0%)	0 (0.0%)	1 (0.7%)
Hypochromic anaemia	1 (1.0%)	0 (0.0%)	1 (0.7%)
Thrombocytosis	1 (1.0%)	0 (0.0%)	1 (0.7%)
Increased tendency to bruise	0 (0.0%)	1 (2.1%)	1 (0.7%)
Pancytopenia	0 (0.0%)	1 (2.1%)	1 (0.7%)
Leukocytosis	1 (1.0%)	0 (0.0%)	1 (0.7%)
Subjects	96 (100.0%)	47 (100.0%)	143 (100.0%)
Denominator	Column total	Column total	(ActiveSubset)

Source: JRevselADSL RANDFL_Y AEDECODbyTRT01AfiltSOC_Blood TRTEMFL_Ycoltot.xls; JRevSelADSL RANDFL_Y AEDECODbyTRT01AfiltSOC_Blood TRTEMFL_Ysubset.xls

Adverse events of interest

Seizure

Two subjects treated with eculizumab had an adverse event of a tonic convulsion. One was a worsening of tonic brainstem seizures which are an established manifestation of NMO and one was a "painful tonic seizure, also likely attributable to the underlying disease.

Hepatobiliary SOC

An AE of DILI was reported for two eculizumab subjects (Table 49). These two subjects are discussed further in 8.4.6 .

Table 49: Adverse Events in the Hepatobiliary SOC, safety population

Dictionary Derived Term	Eculizumab	Placebo
Biliary colic	1 (1.0%)	0 (0.0%)
Cholecystitis	0 (0.0%)	1 (2.1%)
Cholecystitis acute	1 (1.0%)	1 (2.1%)
Cholelithiasis	1 (1.0%)	1 (2.1%)
Drug-induced liver injury	2 (2.1%)	0 (0.0%)
Gallbladder disorder	1 (1.0%)	0 (0.0%)
Hepatic function abnormal	0 (0.0%)	1 (2.1%)
Hyperbilirubinaemia	1 (1.0%)	0 (0.0%)
Subjects(filtered)	4 (4.2%)	3 (6.4%)
1stColItemSubjects	96 (100.0%)	47 (100.0%)

Source: JRevselADSLSAFFL_Y ADSLTRT01AbyAEDECODfiltSOC_HEPBIL.xls

ODE 1 analysis of AE groups

Analysis using the Office of Drug Evaluation 1 (ODE1) adverse event term groups is listed in Table 50 below. The results are consistent with the analyses earlier in this review.

Table 50: ODE1 adverse event groups, eculizumab ≥ 2% and greater than placebo

ODE1 adverse event group	Eculizumab		Placebo	
	N	%	N	%
Infection, all	72	75	32	68.1
URI, cold, rhinitis, upper respiratory tract infection, flu-like illness	49	51	16	34
Infection, viral	25	26	7	14.9
Diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-difficile	19	19.8	9	19.1
Eye other	17	17.7	6	12.8
Dizziness, light-headedness	14	14.6	6	12.8
Leukopenia (neutropenia and/or lymphopenia)	12	12.5	2	4.26
Arthralgia, arthritis, arthrosis	12	12.5	5	10.6
Influenza	11	11.5	2	4.26
Bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	11	11.5	4	8.51
Constipation	9	9.38	3	6.38
Paresthesia, hypoaesthesia	8	8.33	3	6.38
Herpes virus	7	7.29	3	6.38
Anxiety, nervousness, panic attacks	7	7.29	2	4.26
GOT, GPT, GGTP, Lfts	7	7.29	3	6.38

ODE1 adverse event group	Eculizumab		Placebo	
	N	%	N	%
Cataract	6	6.25	2	4.26
Visual disturbance	6	6.25	2	4.26
Cellulitis, erysipelas	5	5.21	1	2.13
Hypertension, BP increased	5	5.21	2	4.26
Diabetes, glucose intolerance, hyperglycemia, hba1c, glycosuria, ketones	5	5.21	1	2.13
Fe (iron) Deficiency	5	5.21	2	4.26
Lymphopenia	5	5.21	1	2.13
Cramps, muscle spasm	5	5.21	2	4.26
Anorexia, decreased appetite	5	5.21	1	2.13
Hematuria	4	4.17	1	2.13
Abscess, boil, furuncle	3	3.13	1	2.13
Weight gain	3	3.13	1	2.13

Source: Final ODE1 datatable Study 301.jmp

Depression

One subject in the eculizumab group and 5 (10.6%) in the placebo group had an AE in the depression grouping. One subject in the eculizumab group had an AE in the suicidal ideation group.

8.4.6. Laboratory Findings

Chemistry

There were no significant changes in any electrolyte in either treatment group. Using the ODE1 AE groups, there was one subject in the eculizumab group with an AE of hypokalemia and 2 in the placebo group. There were no other subjects with an AE in any other AE group related to electrolytes.

There were no significant changes in measures of renal function. Using the ODE1 AE groups, there was one subject in the eculizumab group and 3 in the placebo group with an AE related to renal function.

Changes in liver transaminases were relatively uncommon and transient. For any given visit, elevations of transaminases were consistently more common in the eculizumab group. One eculizumab subject had one AST value >5X ULN (ECU-NMO-301 (b) (6) – ADY 182) – this corresponded to an AE of fever and headache on day 181 – both were mild and resolved completely. Two eculizumab subjects had a single elevation of ALT >5X ULN. Three additional eculizumab subjects had an elevation of 3X ULN (ECU-NMO-301 (b) (6), ECU-NMO-301- (b) (6), and ECU-NMO-301- (b) (6). These were also transient and without symptoms. There were no bilirubin values > 2X ULN and there were no subjects who met Hy's Law criteria.

Using the ODE1 AE groups, there was an AE related to AST, ALT, GGTP or "LFT" in 7.29% of the eculizumab group and in 6.38% of the placebo group.

Table 51: AST shift from baseline, safety population

	Eculizumab			Placebo
AST_Post_Base_Category	Base AST Normal	Base AST > ULN <=2xULN	Base AST > 2xULN <=3xULN	Base AST Normal
AST > ULN <=2xULN	15 (15.6%)	0 (0.0%)	0 (0.0%)	8 (17.0%)
AST > 2xULN <=3xULN	2 (2.1%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
AST > 3xULN <=5xULN	1 (1.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)
AST > 5xULN <=10xULN	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Subjects(filtered)	18 (18.8%)	3 (3.1%)	1 (1.0%)	8 (17.0%)
1stCollItemSubjects	96 (100.0%)	96 (100.0%)	96 (100.0%)	47 (100.0%)

Source: JRevselADSLSAFFL_Y ASTshiftfomBL worsenonly.xls

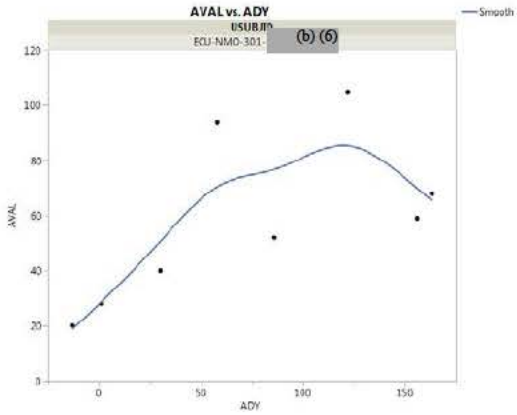
Table 52: ALT shift from baseline, safety population

	Eculizumab			Placebo	
ALT_Post_Base_Category	Base ALT Normal	Base ALT > ULN <=2xULN	Base ALT > 3xULN <=5xULN	Base ALT Normal	Base ALT > ULN <=2xULN
ALT > ULN <=2xULN	16 (16.7%)	0 (0.0%)	0 (0.0%)	7 (14.9%)	0 (0.0%)
ALT > 2xULN <=3xULN	3 (3.1%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
ALT > 3xULN <=5xULN	3 (3.1%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ALT > 5xULN <=10xULN	0 (0.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)
Subjects(filtered)	22 (22.9%)	3 (3.1%)	1 (1.0%)	7 (14.9%)	1 (2.1%)
1stCollItemSubjects	96 (100.0%)	96 (100.0%)	96 (100.0%)	47 (100.0%)	47 (100.0%)

Source: JRevselADSLSAFFL_Y ALTshiftfromBLworsenonly.xls

There were two subjects with an AE of Drug-induced liver failure. One of these subjects was one of the subjects described above with a transient increase in transaminases (301-(b) (6) but the second such subject (301-(b) (6) did not have an elevation greater than 3X. The change was attributed to azathioprine, which was discontinued (Figure 6).

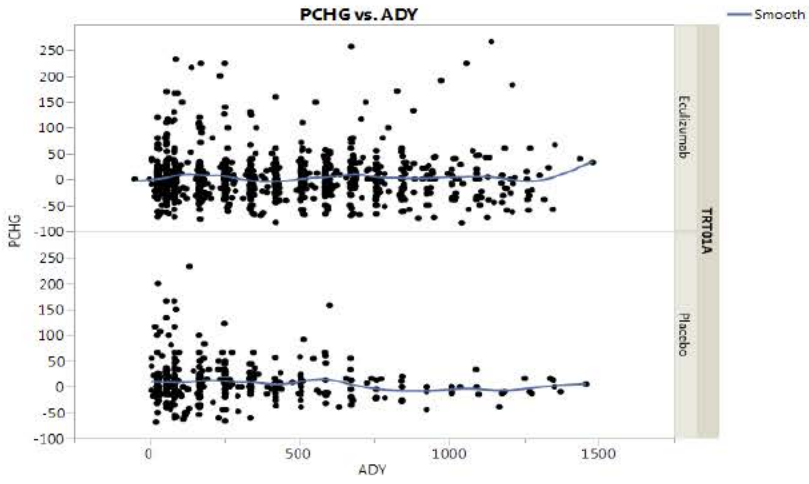
Figure 6: AST by study day, subject 301-(b) (6)



Hematology

There were no consistent changes in leucocyte or lymphocytes blood cell counts during treatment with eculizumab compared to placebo. The percent change in the lymphocyte count by relative study day is shown in **Figure 7** below. Using the ODE1 AE groups, an AE in the leucopenia, lymphopenia occurred in 12.5% (12 subjects) in the eculizumab group compared to 4.26% of the placebo group.

Figure 7: Percent change in lymphocyte count by study day, safety population



8.4.7. Vital Signs

The incidence of vital signs that met pre-specified criteria for abnormal values is shown in Table 53. There were no major differences between treatment groups. A systolic blood pressure below 90 mmHg was somewhat more common in the eculizumab group.

Table 53: Critical vital signs, safety population

	Eculizumab	Placebo
SBP		
SBP < 90 mmHg	19 (19.8%)	3 (6.4%)
SBP > 140 mmHg	32 (33.3%)	19 (40.4%)
SBP > 160 mmHg	6 (6.3%)	4 (8.5%)
DBP		
DBP < 50 mmHg	10 (10.4%)	3 (6.4%)
DBP > 90 mmHg	30 (31.3%)	14 (29.8%)
DBP > 100 mmHg	7 (7.3%)	2 (4.3%)
HR		
Heart Rate < 60 beats/min	30 (31.3%)	10 (21.3%)
Heart Rate > 100 beats/min	30 (31.3%)	11 (23.4%)
Temperature		
Body Temperature < 36 C	39 (40.6%)	12 (25.5%)
Body Temperature > 38 C	0	0
Weight		
>= 7% decrease from Baseline	15 (15.6%)	6 (12.8%)
>= 7% increase from Baseline	26 (27.1%)	12 (25.5%)
Total population	96 (100%)	47 (100%)

Using the ODE1 adverse event groupings, the incidence of an AE of hypertension was 5.21% (5 subjects) for the eculizumab group and 4.26% (2 subjects) for the placebo group. The hypotension grouping included 2.08% of the eculizumab group and 4.26% of the placebo group. Orthostasis was reported in 1.04% of the eculizumab group and in 4.26% of the placebo group. There were 2 eculizumab subjects in the pre-syncope/syncope group and one in the placebo group.

8.4.8. Electrocardiograms (ECGs)

There were no consistent abnormal ECG findings during eculizumab treatment. Using the ODE1 AE groupings, any arrhythmia-related AE occurred in 3.13% of the eculizumab group and in 4.26% of the placebo group.

8.4.9. QT

There were no consistent and sustained alterations of the QT interval. One subject in the eculizumab treatment group had a QTcF increase of >60 msec on two occasions – days 365 and 394 (and over 500 msec on day 394) but returned to normal at EOS. Three subjects had an

increase in QTcB of > 60 msec. One is the same subject who had the transient increase in QTcF. The remaining 2 subjects did not have an increase in QTcF of 60 msec. Using the ODE1 AE groups, there were no events of QT prolongation in either treatment group.

Table 54: Change from baseline, QTcF, safety population

Change from Baseline Category 1	Eculizumab	Placebo
Change from BL <= 0 msec	63 (65.6%)	21 (44.7%)
Change from BL > 0 to <= 30 msec	48 (50.0%)	27 (57.4%)
Change from BL > 30 to <= 60 msec	12 (12.5%)	5 (10.6%)
Change from BL > 60 msec	1 (1.0%)	0 (0.0%)
Subjects(filtered)	95 (99.0%)	47 (100.0%)
1stCollItemSubjects	96 (100.0%)	47 (100.0%)

Source: JRevselADSLSAFFL_Y CHGCAT1byTRT01AfiltPARAM_QTcF.xls

Table 55: Change from baseline, QTcB, safety population

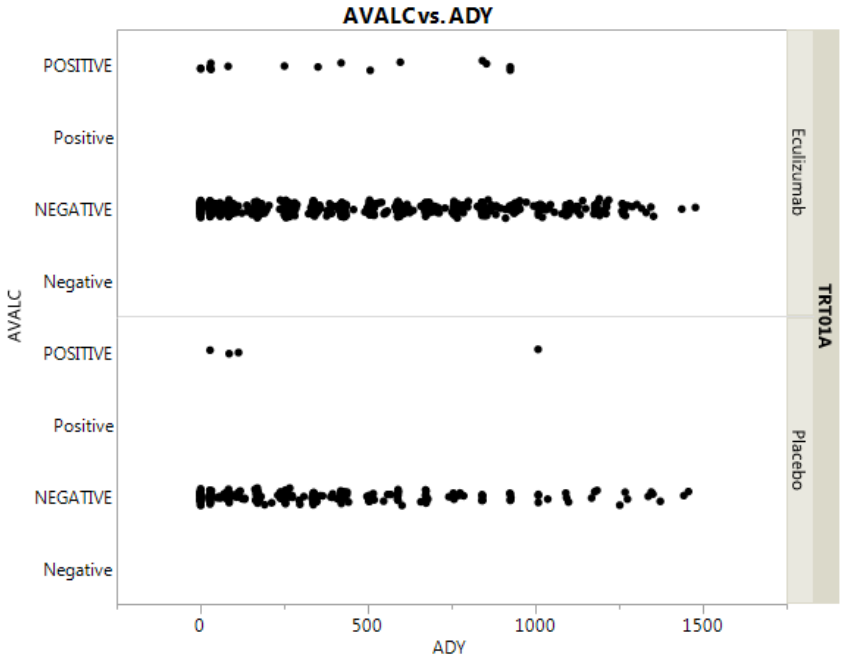
Change from Baseline Category 1	Eculizumab	Placebo
Change from BL <= 0 msec	62 (64.6%)	21 (44.7%)
Change from BL > 0 to <= 30 msec	39 (40.6%)	24 (51.1%)
Change from BL > 30 to <= 60 msec	14 (14.6%)	11 (23.4%)
Change from BL > 60 msec	3 (3.1%)	0 (0.0%)
Subjects(filtered)	95 (99.0%)	47 (100.0%)
1stCollItemSubjects	96 (100.0%)	47 (100.0%)

Source: JRevselADSLSAFFL_Y CHGCAT1byTRT01AfiltPARAM_QTcB.xls

8.4.10. Immunogenicity

Anti-drug antibodies were relatively infrequent over the course of the trial (Figure 8). Neutralizing antibodies were not detected.

Figure 8: Anti-drug antibodies by study day



Source: ADA Subset of Immunogenicity Subset of ADLB 301.jmp

8.5. Analysis of Submission-Specific Safety Issues

The sponsor included a flag for adverse events of special interest in the ADAE dataset. The categories of cardiac events and angioedema did not reveal a safety concern for these types of events during eculizumab treatment.

8.5.1. Serious infections

Infection with encapsulated microorganisms is a specific concern during treatment with eculizumab. Soliris carries a black box warning for serious meningococcal infections. Subjects in the NMO study were required to be vaccinated for meningococcal disease at least two weeks prior to treatment. There were no reports of meningococcal infection during study 301 or the open label extension. There were no reports of gonococcal infections. Infections with Aspergilla have also been reported during treatment for other indications, but no aspergilla infections were reported during the NMOSD studies.

The sponsor included a flag for “other serious infections” in the ADAE dataset. There were 14 events in this category in 12 eculizumab subjects (14.6%) and 8 events in 6 placebo subjects (12.8%) (**Table 56**).

Reviewer Comment: A review of the narratives for the events in Table 54 did not suggest that encapsulated organisms were the dominant pathogen.

Table 56: Other Serious infection, safety population

Dictionary Derived Term	Eculizumab	Placebo
Appendicitis	1 (1.0%)	0 (0.0%)
Bartholin's abscess	1 (1.0%)	0 (0.0%)
Bronchitis	1 (1.0%)	1 (2.1%)
Cellulitis	2 (2.1%)	0 (0.0%)
Gallbladder empyema	1 (1.0%)	0 (0.0%)
Gastroenteritis viral	0 (0.0%)	1 (2.1%)
Herpes zoster	0 (0.0%)	1 (2.1%)
Infectious pleural effusion	1 (1.0%)	0 (0.0%)
Influenza	1 (1.0%)	1 (2.1%)
Pneumococcal infection	0 (0.0%)	1 (2.1%)
Pneumonia	3 (3.1%)	1 (2.1%)
Renal abscess	1 (1.0%)	0 (0.0%)
Urinary tract infection	2 (2.1%)	0 (0.0%)
Viral upper respiratory tract infection	0 (0.0%)	1 (2.1%)
Total Subjects	96 (100.0%)	47 (100.0%)

Source: JRevselADSLSAFFL_Y AEDECODbyTRT01AfiltTRTEMFL_Y OTSINFL_Y.xls

8.5.2. Sepsis

There were 2 events of sepsis during the controlled treatment phase. Both occurred in the eculizumab group. One event in subject (b) (6) was fatal and is described in detail in **8.4.1.** The subject was on concurrent AZA, 50 mg t.i.d. One event in subject (b) (6) started on study day 860 and resolved with appropriate treatment. Subject (b) (6) was on chronic prednisolone, 15 mg/day.

8.5.3. Infusion Reactions

Infusion reactions were infrequent (Table 57). None were considered serious.

Table 57: Infusion reaction flag, safety population

AEDECOD	N(Eculizumab)	N(Placebo)
Dermatitis allergic	1	0
Dermatitis contact	0	1

AEDECOD	N(Eculizumab)	N(Placebo)
Infusion related reaction	2	0
Injection site rash	1	0
Rash	1	0
Rash erythematous	1	0
Rash maculo-papular	0	1

Source: INFUREFL_Y Subset of ADAE By (AEDECOD).jmp

8.6. Safety Analyses by Demographic Subgroups

There are too few subjects in many subgroups to allow a valid conclusion regarding the safety of eculizumab in those groups. The incidence of any non-serious AE by demographic group is listed in Table 58. Where the number of subjects does allow a tentative conclusion, there does not appear to be a demographic subpopulation that is disproportionately vulnerable to adverse events attributable to eculizumab. It does appear that subjects who were being treated with eculizumab alone were less likely to have an AE compared to those who were on concurrent immunosuppressant therapy. The same conclusions apply to the incidence of SAEs (Table 59).

Table 58: Incidence of any non-serious AE by demographic subgroup, safety population

DEMOGRAPHIC GROUP	Eculizumab	Placebo
SEX		
F	79 82.3%)	40 (85.1%)
M	7 (7.3%)	3 (6.4%)
BY AGE GROUP, < 45 YEARS VS. >= 45 YEARS		
< 45 YEARS	40 (41.7%)	23 (48.9%)
>= 45 YEARS	46 (47.9%)	20 (42.6%)
BY AGE GROUP, 18 TO < 65 YEARS VS. >= 65 YEARS		
>= 65 YEARS	6 (6.3%)	3 (6.4%)
18 TO < 65 YEARS	80 (83.3%)	40 (85.1%)
RACE		
AMERICAN INDIAN OR ALASKA NATIVE	1 (1.0%)	0 (0.0%)
ASIAN	33 (34.4%)	13 (27.7%)
BLACK OR AFRICAN AMERICAN	8 (8.3%)	8 (17.0%)
UNKNOWN	1 (1.0%)	0 (0.0%)
WHITE	43 (44.8%)	22 (46.8%)
REGION		
AMERICAS	25 (26.0%)	14 (29.8%)
ASIA-PACIFIC	31 (32.3%)	11 (23.4%)
EUROPE	30 (31.3%)	18 (38.3%)
IST Randomization Stratification		
CHANGES IN IST(S) SINCE LAST RELAPSE AT RANDOMIZATION	31 (32.3%)	17 (36.2%)
CONTINUING ON SAME IST(S) SINCE LAST RELAPSE AT RANDOMIZATION	44 (45.8%)	22 (46.8%)

DEMOGRAPHIC GROUP	Eculizumab	Placebo
TREATMENT NAIVE AT RANDOMIZATION	11 (11.5%)	4 (8.5%)

Source: JRevselADSLSAFFL_Y DemogbyTRT01AfiltTRTEMFL_Y AESER_N.xls

Table 59: Incidence of any serious AE by demographic subgroup, safety population

DEMOGRAPHIC GROUP	Eculizumab	Placebo
SEX		
F	26 (27.1%)	23 (48.9%)
M	4 (4.2%)	3 (6.4%)
BY AGE GROUP, < 45 YEARS VS. >= 45 YEARS		
< 45 YEARS	10 (10.4%)	12 (25.5%)
>= 45 YEARS	20 (20.8%)	14 (29.8%)
BY AGE GROUP, 18 TO < 65 YEARS VS. >= 65 YEARS		
>= 65 YEARS	3 (3.1%)	2 (4.3%)
18 TO < 65 YEARS	27 (28.1%)	24 (51.1%)
BY RACE		
ASIAN	13 (13.5%)	12 (25.5%)
BLACK OR AFRICAN AMERICAN	4 (4.2%)	3 (6.4%)
UNKNOWN	1 (1.0%)	0 (0.0%)
WHITE	12 (12.5%)	11 (23.4%)
BY REGION		
AMERICAS	11 (11.5%)	5 (10.6%)
ASIA-PACIFIC	13 (13.5%)	10 (21.3%)
EUROPE	6 (6.3%)	11 (23.4%)
BY IST STRATUM		
CHANGES IN IST(S) SINCE LAST RELAPSE AT RANDOMIZATION	11 (11.5%)	8 (17.0%)
CONTINUING ON SAME IST(S) SINCE LAST RELAPSE AT RANDOMIZATION	17 (17.7%)	14 (29.8%)
TREATMENT NAIVE AT RANDOMIZATION	2 (2.1%)	4 (8.5%)

Source: JRevselADSLSAFFL_Y DemogbyTRT01AfiltTRTEMFL_Y AESER_Y.xls

Reviewer Comment: It may be expected that patients being treated with a combination of drugs that interfere with more than one aspect of the immune system may be exposed to an increased risk of infection.

By SOC

Sex

There are not enough males in any SOC to draw a valid conclusion about susceptibility to AEs by sex. There is no clear safety signal for any SOC, including infections and Infestations.

Race

The only racial groups with an adequate number of subjects were the Asian and White groups. There is no clear safety signal for any SOC, including infections and Infestations.

Age group, less than 45 vs. 45 and older, and 18 to less than 65 vs. 65 and over

These is a fairly equal distribution of subjects over and under 45 years old. For that comparison, where there is an adequate number of events, there is no indication of disproportionate risk by the 45-year old age cut-off. The same is the case for the 65-year old cut-off.

Region/Country

There is no indication of a disproportionate number of AEs by region. There are too few observations to draw any conclusions about specific countries.

8.7. Specific Safety Studies/Clinical Trials

There were no studies dedicated to safety alone.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There are infrequent events applicable to the risk of neoplasms.

8.8.2. Human Reproduction and Pregnancy

There is one observation relevant to reproduction:

Subject (b) (6)

EXPOSURE VIA SEMEN (Exposure via body fluid) and PRETERM (35 WEEKS) [Premature baby 33 to 36 weeks]

On (b) (6) (Study Day 423), while on study drug (eculizumab), the patient's partner reported that she was pregnant. It was noted that no contraceptive methods were used prior to the pregnancy. Her last menstrual cycle had begun on (b) (6) (Study Day 389). On (b) (6) (Study Day 630), the patient's partner gave birth by Cesarean section to a female infant: gestational age 35 weeks, weight 3.330 kg, length 48.3 cm, and APGAR scores of 8 at first and second check. The infant, who had no malformations

or abnormalities noted at birth, was admitted to the intensive care unit for jaundice, being premature, and being at risk for congenital hip dysplasia. The infant started breastfeeding on (b) (6) (Study Day 634). No further information is available regarding the infant.

The patient continued to receive study drug (eculizumab) in the study.

8.8.3. Pediatrics and Assessment of Effects on Growth

Study 301 did not include any pediatric subjects.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no instances of overdose of eculizumab. Abuse is not expected and therefore not addressed for this monoclonal antibody. There are no data at this time to assess the effect of discontinuation of eculizumab on the occurrence of NMOSD relapses.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There is no postmarket experience with eculizumab treatment of NMOSD. For the currently approved indications, the primary concern remains the occurrence of infections with encapsulated organisms, especially with Neisseria meningitis. Disseminated gonococcal infections have also been reported. Aspergilla infections have been reported. Infusion-related reactions are a potential concern but have generally not been serious for the approved indications.

8.9.2. Expectations on Safety in the Postmarket Setting

The safety of eculizumab for the treatment of NMOSD is not expected to differ greatly from that for other indications. The concern for hemolysis on withdrawal of treatment for PNH and for thrombotic microangiopathy on withdrawal of treatment for aHUS are not expected to be concerns for discontinuation of treatment for NMOSD. Surveillance for any exacerbation of relapses will be needed on discontinuation of treatment for NMOSD.

8.9.3. Additional Safety Issues From Other Disciplines

There are no specific additional safety concerns based on the nonclinical or Clinical Pharmacology reviews up to the time of this review.

8.10. Integrated Assessment of Safety

The Safety update, submitted in sequence 0665, serves as the ISS since it includes all subjects

who continued into the open label extension study. Safety data from Study 302, at the time of the BLA submission, did not include the subjects who entered the study after completion of Study 301 without having a relapse. The population at the time of the safety update included 137 subjects, 96 treated with eculizumab in period one and 41 treated with placebo in period one. The definitions for the 3 treatment periods are listed in Table 60.

Table 60: Treatment periods for ISS safety update

Period	Start	Stop
01	Screening of ECU-NMO-301	The day before first dose of ECU-NMO-302
02	First dose of ECU-NMO-302	End of study or discontinuation, or data cutoff date of ECU- NMO-302
03	If subjects were randomized in Eculizumab in ECU-NMO-301, then the screening of ECU-NMO- 301; if subjects were randomized into Placebo in ECU-NMO-301, then the first dose date of ECU- NMO-302	End of study or discontinuation of ECU-NMO-302

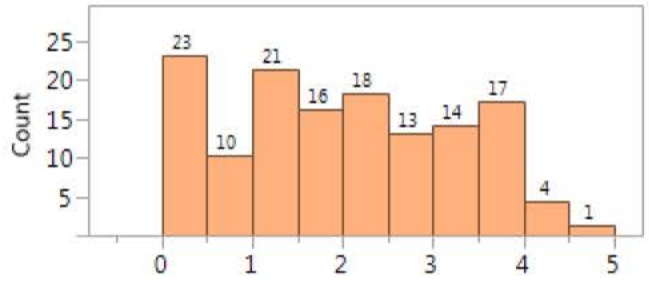
The total exposure to eculizumab treatment from the first dose in the RCT to the end of study or discontinuation was 279.3 subject years. The mean duration of treatment was 737±445 days. Treatment duration was for greater than one year for 104 subjects (Figure 9).

Table 61: Treatment duration for ISS safety update

	Eculizumab treatment duration periods 1 + 2 (TRTDUR3) (days)					
TRT03A	N Rows	Mean	Std Dev	Min	Max	Median
Eculizumab	137	737.4	444.8	1	1665	693

Source: SAF03FL_Y Subset of ADSL ISS update STUPDUR3 By (TRT03A).jmp

Figure 9: Treatment duration, years, ISS safety update population



The incidence of serious and non-serious adverse events did not change over the extended period of observation to the end of Study 302 (Table 62). The most common non-serious adverse event terms for the full period of observation ("period 3" in Table 60 above) were essentially unchanged from the RCT period (Table 62).

Table 62: Serious and non-serious adverse events by study period, safety population

Serious Event Y/N	Eculizumab		
	Period 3[a]	Period 2[b]	Period 1[c]
Not serious	125 (91.2%)	111 (93.3%)	125 (91.2%)
Serious	64 (46.7%)	56 (47.1%)	64 (46.7%)
Subjects(filtered)	137 (100.0%)	119 (100.0%)	137 (100.0%)
1stColltemSubjects	137 (100.0%)	119 (100.0%)	137 (100.0%)

[a]: **Source:** JRevselADSLSAF03FL_Y AESERbyTRT03A.xls
[b]: **Source:** JRevselADSLSAF02FL_Y AESERbyTRT03A.xls
[c]: **Source:** JRevselADSLSAF01FL_Y AESERbyTRT03A.xls

The distribution of adverse events by SOC is listed in Table 63 below. There is no change in this distribution compare to periods 1 and 2.

Table 63: Adverse events by SOC, period 3

Body System or Organ Class	Eculizumab
Blood and lymphatic system disorders	36 (26.3%)
Cardiac disorders	12 (8.8%)
Ear and labyrinth disorders	16 (11.7%)
Endocrine disorders	7 (5.1%)
Eye disorders	36 (26.3%)
Gastrointestinal disorders	79 (57.7%)
General disorders and administration site conditions	51 (37.2%)
Hepatobiliary disorders	10 (7.3%)
Immune system disorders	6 (4.4%)
Infections and infestations	113 (82.5%)
Injury, poisoning and procedural complications	61 (44.5%)
Investigations	35 (25.5%)
Metabolism and nutrition disorders	28 (20.4%)
Musculoskeletal and connective tissue disorders	76 (55.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (9.5%)
Nervous system disorders	85 (62.0%)
Psychiatric disorders	32 (23.4%)
Renal and urinary disorders	32 (23.4%)
Reproductive system and breast disorders	20 (14.6%)
Respiratory, thoracic and mediastinal disorders	50 (36.5%)
Skin and subcutaneous tissue disorders	55 (40.1%)
Social circumstances	1 (0.7%)
Surgical and medical procedures	2 (1.5%)
Vascular disorders	26 (19.0%)
Subjects(filtered)	137 (100.0%)
1stCollItemSubjects	137 (100.0%)

Table 64: Dictionary derived non-serious adverse event terms, 10% of more, period 3 safety population

Dictionary Derived Term	Eculizumab
Headache	42 (30.7%)
Upper respiratory tract infection	39 (28.5%)
Nasopharyngitis	34 (24.8%)
Urinary tract infection	29 (21.2%)
Nausea	28 (20.4%)
Diarrhoea	25 (18.2%)
Pain in extremity	25 (18.2%)
Back pain	24 (17.5%)
Neuromyelitis optica spectrum disorder	24 (17.5%)
Arthralgia	23 (16.8%)

Dictionary Derived Term	Eculizumab
Dizziness	21 (15.3%)
Cough	18 (13.1%)
Influenza	18 (13.1%)
Vomiting	17 (12.4%)
Fatigue	17 (12.4%)
Constipation	16 (11.7%)
Bronchitis	16 (11.7%)
Contusion	16 (11.7%)
Conjunctivitis	16 (11.7%)
Pyrexia	15 (10.9%)
Pharyngitis	15 (10.9%)
Paraesthesia	15 (10.9%)

Source: JRevselADSLSAF03FL_Y AEDECODbyTRT03Adesc.xls

Reviewer Comment: There are no new safety signals on review of all of the adverse events for the full period of observation.

Subgroups

There remains a suggestion that those with higher disability as measured by the EDSS score at baseline may be at higher risk for adverse events, especially for infections, both non-serious (Table 65) and serious (Table 66).

Table 65: Nonserious adverse events, safety update population, by baseline EDSS group

Body System or Organ Class	Eculizumab		Subjects(filtered)
	Baseline EDSS dichotomized		
	High	Low	
Blood and lymphatic system disorders	22 (16.1%)	14 (10.2%)	36 (25.2%)
Cardiac disorders	9 (6.6%)	3 (2.2%)	12 (8.4%)
Ear and labyrinth disorders	10 (7.3%)	6 (4.4%)	16 (11.2%)
Endocrine disorders	4 (2.9%)	3 (2.2%)	7 (4.9%)
Eye disorders	24 (17.5%)	12 (8.8%)	36 (25.2%)
Gastrointestinal disorders	48 (35.0%)	31 (22.6%)	79 (55.2%)
General disorders and administration site conditions	35 (25.5%)	16 (11.7%)	51 (35.7%)
Hepatobiliary disorders	7 (5.1%)	3 (2.2%)	10 (7.0%)
Immune system disorders	5 (3.6%)	1 (0.7%)	6 (4.2%)
Infections and infestations	64 (46.7%)	49 (35.8%)	113 (79.0%)
Injury, poisoning and procedural complications	44 (32.1%)	17 (12.4%)	61 (42.7%)
Investigations	26 (19.0%)	9 (6.6%)	35 (24.5%)
Metabolism and nutrition disorders	19 (13.9%)	9 (6.6%)	28 (19.6%)
Musculoskeletal and connective tissue disorders	46 (33.6%)	30 (21.9%)	76 (53.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (3.6%)	8 (5.8%)	13 (9.1%)

Body System or Organ Class	Eculizumab		Subjects(filtered)
	Baseline EDSS dichotomized		
	High	Low	
Nervous system disorders	53 (38.7%)	32 (23.4%)	85 (59.4%)
Psychiatric disorders	21 (15.3%)	11 (8.0%)	32 (22.4%)
Renal and urinary disorders	21 (15.3%)	11 (8.0%)	32 (22.4%)
Reproductive system and breast disorders	11 (8.0%)	9 (6.6%)	20 (14.0%)
Respiratory, thoracic and mediastinal disorders	25 (18.2%)	25 (18.2%)	50 (35.0%)
Skin and subcutaneous tissue disorders	30 (21.9%)	25 (18.2%)	55 (38.5%)
Social circumstances	0 (0.0%)	1 (0.7%)	1 (0.7%)
Surgical and medical procedures	2 (1.5%)	0 (0.0%)	2 (1.4%)
Vascular disorders	18 (13.1%)	8 (5.8%)	26 (18.2%)
Subjects(filtered)	78 (56.9%)	59 (43.1%)	143 (100.0%)
1stColItemSubjects	137 (100.0%)	137 (100.0%)	(Denom=1stColTot)

Source: JRevselADSLSAF03FL_Y SOCbyTRT03AandDICHOTBLEDSS.xls

Table 66: Serious adverse events, safety update population, by baseline EDSS category

Body System or Organ Class	Eculizumab		Subjects(filtered)
	Baseline EDSS Dichotomized		
	High	Low	
Blood and lymphatic system disorders	2 (1.5%)	0 (0.0%)	2 (1.4%)
Cardiac disorders	2 (1.5%)	0 (0.0%)	2 (1.4%)
Ear and labyrinth disorders	0 0.0%)	1 (0.7%)	1 (0.7%)
Eye disorders	3 (2.2%)	1 (0.7%)	4 (2.8%)
Gastrointestinal disorders	4 (2.9%)	1 (0.7%)	5 (3.5%)
General disorders and administration site conditions	3 (2.2%)	1 (0.7%)	4 (2.8%)
Hepatobiliary disorders	3 (2.2%)	0 (0.0%)	3 (2.1%)
Infections and infestations	17 (12.4%)	8 (5.8%)	25 (17.5%)
Injury, poisoning and procedural complications	8 (5.8%)	0 (0.0%)	8 (5.6%)
Investigations	2 (1.5%)	0 (0.0%)	2 (1.4%)
Metabolism and nutrition disorders	1 (0.7%)	1 (0.7%)	2 (1.4%)
Musculoskeletal and connective tissue disorders	4 (2.9%)	2 (1.5%)	6 (4.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.5%)	1 (0.7%)	3 (2.1%)
Nervous system disorders	21 (15.3%)	7 (5.1%)	28 (19.6%)
Psychiatric disorders	2 (1.5%)	1 (0.7%)	3 (2.1%)
Renal and urinary disorders	1 (0.7%)	0 (0.0%)	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	5 (3.6%)	1 (0.7%)	6 (4.2%)
Surgical and medical procedures	2 (1.5%)	0 (0.0%)	2 (1.4%)
Vascular disorders	4 (2.9%)	0 (0.0%)	4 (2.8%)
Subjects(filtered)	47 (34.3%)	17 (12.4%)	143 (100.0%)
1stColItemSubjects	137 (100.0%)	137 (100.0%)	(Denom=1stColTot)

Source: JRevselADSLSAF03FL_Y SOCbyTRT03AandDICHOTBLEDSSfiltAESERFL_Y.xls

9. Advisory Committee Meeting and Other External Consultations

Advisory Committee not recommended.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Recommend modifications to multiple sections – see the final agreed labeling.

10.2. Nonprescription Drug Labeling – N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

The REMS for the currently approved indications should now include the indication for NMOSD. No modifications of the current REMS are necessary.

12. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study 301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 140		
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): 0		
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: _____ Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 8		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. 2006 Diagnostic Criteria for NMO[21]

Definite NMO

Optic Neuritis
Acute Myelitis
At least two of three supportive criteria

1. Contiguous spinal cord MRI lesion extending over 3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-IgG seropositive status

13.4. 2007 Diagnostic Criteria for NMO Spectrum Disorder[22]

Neuromyelitis optica
Limited forms of neuromyelitis optica

- Idiopathic single or recurrent events of longitudinally extensive myelitis (≥ 3 vertebral segment spinal cord lesion seen on MRI
- Optic neuritis: recurrent or simultaneous bilateral Asian optic-psinal multiple sclerosis

Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease
Optic neuritis or myelitis associated with brain lesions typical of neuromyelitis optica (hypothalamic, corpus callosal, periventricular, or brainstem)

13.5. 2015 Consensus Diagnostic Criteria for NMOSD[9]

NMOSD with AQP4-IgG
At least one core clinical characteristic
Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended

NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status

- At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
    - At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
    - Dissemination in space (2 or more different core clinical characteristics)
    - Fulfillment of additional MRI requirements, as applicable

- Negative tests for AQP4-IgG using best available detection method, or testing unavailable
- Exclusion of alternative diagnoses

13.6. Eligibility criteria

Inclusion criteria

1. Male or female patients ≥ 18 years old.
2. Diagnosis of NMO as defined by 2006 Criteria by Wingerchuk et al, (**13.3**), or NMOSD as defined by 2007 Criteria by Wingerchuk et al (**13.4**).
3. NMO-IgG seropositive
4. Historical Relapse (as defined by this protocol) of at least 2 relapses in last 12 months or 3 relapses in the last 24 months with at least 1 relapse in the 12 months prior to screening
5. EDSS score ≤7
6. If a patient enters the trial receiving IST(s) for relapse prevention, the patient must be on a stable maintenance dose of IST(s), as defined by the Treating Physician, prior to screening and must remain on that dose for the duration of the study, unless the patient experiences a relapse.
7. Patients must give written informed consent
8. Patients must be willing and able to comply with the protocol requirements for the duration of the trial
9. Female patients of child-bearing potential must have a negative pregnancy test (serum human chorionic gonadotropin [HCG]). Patients must practice an effective, reliable and medically approved contraceptive regimen during the trial and for up to 5 months following discontinuation of treatment.

Exclusion criteria

1. Use of rituximab 3 months prior to screening
2. Use of mitoxantrone 3 months prior to screening
3. Use of IVIg within 3 weeks prior to screening
4. If a patient enters the trial receiving oral corticosteroid(s) with or without other IST(s), the daily corticosteroid dose must be no more than prednisone 20 mg/day (or equivalent) prior to the screening, and must remain on that dose for the duration of the study or until the patient experiences a relapse
5. Pregnant, breastfeeding, or intending to conceive during the course of the trial
6. Unresolved meningococcal disease

7. Any systemic bacterial or other infection which is clinically significant in the opinion of the Investigator and has not been treated with appropriate antibiotics
8. Participation in any other investigational drug study or exposure to an investigational drug or device within 30 days of screening
9. Has previously received treatment with eculizumab
10. Hypersensitivity to murine proteins or to one of the excipients of eculizumab
11. Any medical condition that, in the opinion of the Investigator, might interfere with the patient's participation in the trial, poses any added risk for the patient, or confounds the assessment of the patients

13.7. Schedule of assessments

Schedule of Assessments – Screening Period[1]

Trial Visit	V1
Screening Period Duration	**1-6 Weeks**
Informed Consent[2]	X
Medical History and Demography	X
NMO History[3]	X
Physical Examination[4]	X
Weight and Height	X
Vital Signs[5]	X
Electrocardiogram (ECG)[6]	X
Concomitant Medications[7]	X
Adverse Events (AEs)[8]	
Clinical Laboratory Tests[9]	X
Pregnancy test (serum)[10]	X
NMO-IgG (serum)[11]	X
NMO-IgG (CSF)[12]	
PK/PD/Free C5 (serum)[11]	
PK/C5 (CSF)[12]	
EuroQol (EQ-5D)[13]	
Short Form Health Survey (SF-36)[13]	

Trial Visit	V1
Screening Period Duration	**1-6 Weeks**
Columbia-Suicide Severity Rating Scale (C-SSRS)[15]	
Expanded Disability Status Scale (EDSS)[14]	X
Modified Rankin Scale (mRS)[15]	
Patient Education Card and NMO Symptom Evaluation[15]	X
Neurologic Examination[14, 15]	X
Optic Spinal Impairment Score (OSIS)[15]	
Snellen chart[15]	X
Hauser Ambulation Index (HAI)[15]	X
Medically indicated tests[16]	
Review Inclusion / Exclusion criteria[15]	X
Randomization[17]	
N. meningitidis vaccination[18]	X
Patient Safety Identification Card[18]	
Investigational Product (IP) Infusion[19]	

Schedule of Assessments – Study Period (Visit 2 – Visit 17)

	Induction Phase					Maintenance Phase										
Trial Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**
Trial Week	**Day1**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**
Informed Consent[2]																
Medical History and Demography																
NMO History[3]																
Physical Examination[4]																

	Induction Phase					Maintenance Phase										
Trial Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**
Trial Week	**Day1**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**
Weight and Height																
Vital Signs [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG) [6]																
Concomitant Medications [7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs) [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests [9]	X				X		X		X						X	
Pregnancy test (serum) [10]	X				X		X		X						X	
NMO-IgG (serum) [11]	X				X		X		X						X	
NMO-IgG (CSF) [12]	X								X						X	
PK/PD/Free C5 (serum) [11]	B/P				T/P		T/P		T/P						T/P	
HAHA (serum) [11]	X				X				X						X	
PK/Free C5 (CSF) [12]	X								X						X	
EuroQol (EQ-5D) [13]	X				X		X		X						X	
Short Form Health Survey (SF-36) [13]	X				X		X		X						X	
(C-SSRS) [15]	X				X		X		X						X	
Expanded Disability Status Scale (EDSS) [14]	X				X		X		X						X	
Modified Rankin Scale (mRS) [15]	X				X		X		X						X	
Patient Education Card and NMO Symptom Evaluation [15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Induction Phase					Maintenance Phase										
Trial Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**
Trial Week	**Day1**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W22**	**W24**	**W26**
Neurologic Examination [14, 15]	X				X		X		X						X	
Optic Spinal Impairment Score (OSIS) [15]	X															
Snellen chart [15]	X				X		X		X						X	
Hauser Ambulation Index (HAI) [15]	X				X		X		X						X	
Medically indicated tests [16]																
Review Inclusion / Exclusion criteria [15]	X															
Randomization [17]	X															
N. meningitidis vaccination [18]																
Patient Safety Identification Card [18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product (IP) Infusion [19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Schedule of Assessments – Study Period (Visit 18 – Visit 30)

	Maintenance Phase												
Trial Visit	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**
Trial Week	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**
Informed Consent [2]													
Medical History and Demography													
NMO History [3]													
Physical Examination [4]													
Weight													X

Maintenance Phase													
Trial Visit	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**
Trial Week	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**
Vital Signs [5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG) [6]													X
Concomitant Medications [7]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs) [8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests [9]					X						X		
Pregnancy test (serum) [10]					X						X		
NMO-IgG (serum) [11]					X						X		
NMO-IgG (CSF) [12]											X		
PK/PD/Free C5 (serum) [11]					T/P						T/P		
HAHA (serum) [11]					X						X		
PK/Free C5 (CSF) [12]											X		
EuroQol (EQ-5D) [13]					X						X		
Short Form Health Survey (SF-36) [13]					X						X		
Columbia-Suicide Severity Rating Scale (C-SSRS) [15]					X						X		
Expanded Disability Status Scale (EDSS) [14]					X						X		
Modified Rankin Scale (mRS) [15]					X						X		
Patient Education Card /NMO Symptom Evaluation [15]	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurologic Examination [14, 15]					X						X		
Optic Spinal Impairment Score (OSIS) [15]													
Snellen chart [15]					X						X		
Hauser Ambulation Index (HAI) [15]					X						X		
Medically indicated tests [16]													
Review Inclusion / Exclusion criteria													

Maintenance Phase													
Trial Visit	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**
Trial Week	**W28**	**W30**	**W32**	**W34**	**W36**	**W38**	**W40**	**W42**	**W44**	**W46**	**W48**	**W50**	**W52**
Randomization[17]													
N. meningitidis vaccination[18]													
Patient Safety Identification Card[18]	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product (IP) Infusion[19]	X	X	X	X	X	X	X	X	X	X	X	X	X

Schedule of Assessments – Study Period (Visit 31 – Visit 43)

Maintenance Phase													
Trial Visit	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**V43**
Trial Week	**W54**	**W56**	**W58**	**W60**	**W62**	**W64**	**W66**	**W68**	**W70**	**W72**	**W74**	**W76**	**W78**
Informed Consent[2]													
Medical History and Demography													
NMO History[3]													
Physical Examination[4]													
Weight and Height													
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)[6]													
Concomitant Medications[7]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs)[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests[9]				X						X			
Pregnancy test (serum)[10]				X						X			

Maintenance Phase													
Trial Visit	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**V43**
Trial Week	**W54**	**W56**	**W58**	**W60**	**W62**	**W64**	**W66**	**W68**	**W70**	**W72**	**W74**	**W76**	**W78**
NMO-IgG (serum)[11]				X						X			
NMO-IgG (CSF)[12]										X			
PK/PD/Free C5 (serum)[11]				T/P						T/P			
HAHA (serum)[11]				X						X			
PK/Free C5 (CSF)[12]										X			
EuroQol (EQ-5D)[13]				X						X			
Short Form Health Survey (SF-36)[13]				X						X			
Columbia-Suicide Severity Rating Scale (C-SSRS)[15]				X						X			
Expanded Disability Status Scale (EDSS)[14]				X						X			

Schedule of Assessments – Study Period (Visit 44 – Visit 52)

Maintenance Phase									
Trial Visit	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50**	**V51**	**V52**
Trial Week	**W80**	**W82**	**W84**	**W86**	**W88**	**W90**	**W92**	**W94**	**W96**
Informed Consent[2]									
Medical History and Demography									
NMO History[3]									
Physical Examination[4]									X
Weight									X

Maintenance Phase									
Trial Visit	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50**	**V51**	**V52**
Trial Week	**W80**	**W82**	**W84**	**W86**	**W88**	**W90**	**W92**	**W94**	**W96**
Vital Signs [5]	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG) [6]									X
Concomitant Medication [7]	X	X	X	X	X	X	X	X	X
Adverse Events [8]	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests [9]			X						X
Pregnancy test (serum) [10]			X						X
NMO-IgG (serum) [11]			X						X
NMO-IgG (CSF) [12]									X
PK/PD/Free C5 (serum) [11]			T/P						T/P
HAHA (serum) [11]			X						X
PK/Free C5 (CSF) [12]									X
EuroQol (EQ-5D) [13]			X						X
Short Form Health Survey (SF-36) [13]			X						X
Columbia-Suicide Severity Rating Scale (C-SSRS) [15]			X						X
Expanded Disability Status Scale (EDSS) [14]			X						X
Modified Rankin Scale (mRS) [15]			X						X
Patient Education Card and NMO Symptom Evaluation [15]	X	X	X	X	X	X	X	X	X
Neurologic Examination [14, 15]			X						X
Optic Spinal Impairment Score (OSIS) [15]									
Snellen chart [15]			X						X
Hauser Ambulation Index (HAI) [15]			X						X

Maintenance Phase									
Trial Visit	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50**	**V51**	**V52**
Trial Week	**W80**	**W82**	**W84**	**W86**	**W88**	**W90**	**W92**	**W94**	**W96**
Medically indicated tests [16]									
Review Inclusion / Exclusion criteria [15]									
N. meningitidis vaccination [18]									
Patient Safety Identification Card [18]	X	X	X	X	X	X	X	X	X
Investigational Product (IP) Infusion [19]	X	X	X	X	X	X	X	X	X

Schedule of Assessments - Study Period (Beyond Visit 52 to EOS / ET)

Maintenance Phase			
Trial Visit	**Short Visit**	**Long Visit**	**End of Study (EOS) / Early Termination (ET) Visit**
Trial Week	**Every 2nd week after Visit 52 until EOS Visit except Long Visits (e.g., Weeks 98, 100, 102, 104, 106, 110, etc...)**	**Every 12th week after Visit 52 until EOS Visit (e.g., Weeks 108, 120, 132, 144, etc...)**	
Physical Examination [4]			X
Weight			X
Vital Signs [5]	X	X	X
Electrocardiogram (ECG) [6]			X
Concomitant Medication [7]	X	X	X
Adverse Events [8]	X	X	X
Clinical Laboratory Tests [9]		X	X
Pregnancy test (serum) [10]		X	X

Maintenance Phase			
Trial Visit	**Short Visit**	**Long Visit**	**End of Study (EOS) / Early Termination (ET) Visit**
Trial Week	**Every 2nd week after Visit 52 until EOS Visit except Long Visits (e.g., Weeks 98, 100, 102, 104, 106, 110, etc...)**	**Every 12th week after Visit 52 until EOS Visit (e.g., Weeks 108, 120, 132, 144, etc...)**	
NMO-IgG (serum) [11]		X	X
NMO-IgG (CSF) [12]		X (every 24th week)	X
PK/PD/Free C5 (serum) [11]		T/P	T/P
HAHA (serum) [11]		X	X
PK/Free C5 (CSF) [12]		X (every 24th week)	X
EuroQol (EQ-5D) [13]		X	X
Short Form Health Survey (SF-36) [13]		X	X
Columbia-Suicide Severity Rating Scale (C-SSRS) [15]		X	X
Expanded Disability Status Scale (EDSS) [14]		X	X
Modified Rankin Scale (mRS) [15]		X	X
Patient Education Card and NMO Symptom Evaluation [15]	X	X	X
Neurologic Examination [14, 15]		X	X
Optic Spinal Impairment Score (OSIS) [15]			
Snellen chart [15]		X	X
Hauser Ambulation Index (HAI) [15]		X	X
Medically indicated tests [16]			
Patient Safety Identification Card [18]	X	X	X
Investigational Product (IP) Infusion [19]	X	X	X

Schedule of Assessments – Safety Follow-Up Period (Post-Treatment)

Assessment	Follow-Up Visit
Trial Week	**+8 W**
Informed Consent [2]	
Medical History and Demography	
NMO History [3]	
Physical Examination [4]	
Weight and Height	
Vital Signs [5]	X
Electrocardiogram (ECG) [6]	
Concomitant Medication [7]	X
Adverse Events (AEs) [8]	X
Clinical Laboratory Tests [9]	
Pregnancy test (serum) [10]	
NMO-IgG (serum) [11]	
NMO-IgG (CSF) [12]	
PK/PD/Free C5 (serum) [11]	
PK/Free C5 (CSF) [12]	
EuroQol (EQ-5D) [13]	
Short Form Health Survey (SF-36) [13]	
Columbia-Suicide Severity Rating Scale (C-SSRS) [15]	X
Expanded Disability Status Scale (EDSS) [14]	
Modified Rankin Scale (mRS) [15]	
Patient Education Card and NMO Symptom Evaluation [15]	X

Assessment	Follow-Up Visit
Trial Week	**+8 W**
Neurologic Examination[14, 15]	
Optic Spinal Impairment Score (OSIS)[15]	
Snellen chart[15]	
Hauser Ambulation Index (HAI)[15]	
Medically indicated tests[16]	
Review Inclusion / Exclusion criteria[15]	
Randomization[17]	
N. meningitidis vaccination[18]	
Patient Safety Identification Card[18]	X
Investigational Product (IP) Infusion[19]	

Footnote	Description
1.	All screening procedures must be completed within 1-6 weeks prior to the randomization at Baseline (Visit 2 [Day 1]). Patients who experience a relapse during the Screening Period will be considered a screening failure. Such patients may be rescreened for enrollment into the trial. See Sections 7.1 and 7.6.1 for additional information.
2.	The patient's signed and dated informed consent form (ICF) must be obtained before conducting any trial procedures. The trial duration for an individual patient in this time-to-event trial will vary, i.e., the trial duration for an individual patient will be determined by the time of relapse or, for those patients who do not have a relapse, by the time of trial closure.
3.	The Treating Physician will review the patient's history and diagnosis and document the following at the Screening Visit: NMO or NMOSD diagnosis date (Wingerchuk et.al., 2006 and 2007; refer to Appendix 1 and Appendix 2); and the number of relapses (onset dates) and the clinical presentation of each relapse (e.g., ON, TM, LETM, brainstem or other). See Sections 7.1 and 7.6.1 for additional information.
4.	Additional Physical Examinations can be performed as medically indicated during the trial at the Investigator's discretion.
5.	Vital signs include assessments of systolic and diastolic blood pressure (BP), temperature, respiration rate (RR) and heart rate (HR). Vital signs will be obtained after the patient has been supine or seated for at least 5 minutes. Ideally, each patient's BP should be measured using the same arm.
6.	ECG will be performed at the protocol specified time points. In addition, ECG may be performed if the Investigator feels it is clinically warranted.

Footnote	Description
7.	Concomitant medications will be recorded at the Screening Visit as described in Section 7.1. Use of concomitant medication will be evaluated during the trial and all new medications or changes to concomitant medications will be recorded.
8.	AEs will be evaluated by the Investigator and recorded at every visit in accordance with the trial protocol as described in Section 12.2.
9.	Clinical laboratory tests (chemistry, hematology and urinalysis) will be performed by a central laboratory. Refer to Appendix 8 for a summary of the clinical laboratory tests to be measured.
10.	Pregnancy test must be performed on all women of childbearing potential at specified time points. Pregnancy test (urine or serum) may also be performed at any time during the trial at the Investigator's discretion. Patients must practice an effective, reliable and medically approved contraceptive regimen during the trial and for up to 5 months following discontinuation of treatment. If a patient or a patient's partner becomes or is found pregnant while in the trial, the Sponsor will be notified in accordance with the trial protocol.
11.	Serum samples for NMO-IgG and trough PK/PD/Free C5/HAHA are to be taken approximately 5-90 minutes before the IP infusion. Peak serum samples for PK, PD and free C5 are to be taken at least 60 minutes after completion of the IP infusion.
12.	Cerebrospinal fluid (CSF) samples for NMO-IgG and PK /Free C5 analyses may be collected from consented patients. Patients may choose not to have CSF samples collected and will still be eligible for trial participation.
13.	The QOL self- assessments (EQ-5D and SF-36) will be performed by the patients before any other trial procedures at all trial visits.
14.	The blinded EDSS Rater will perform the Kurtzke neurological assessment and document the FSS and EDSS score. See Section 7.4.6 for more detail.
15.	The Treating Physician will be responsible for overall patient management including patient eligibility evaluation, the supervision of the blinded IP administration, the recording and treating of AEs and the monitoring of safety assessments. The Treating Physician will determine if a patient experiences an On-Trial Relapse and treat the patient's relapse as needed (see recommended On-Trial Relapse Treatment regimen in Section 9.2.1.3). The Treating Physician will assess the patient for any signs or symptoms indicative of relapse at every visit, perform a complete neurologic examination at the specified time points during the trial, and document the OSIS. The Treating Physician or appropriately trained designee will perform the mRS, the visual acuity (VA) test (Snellen chart), the HAI and the C-SSRS.
16.	If medically indicated for evaluation of relapse, additional tests (e.g., MRI, CT scan, laboratory tests, etc.) may be performed at the discretion of the Investigator. If additional medically indicated tests/procedures are performed, the results must be recorded in the eCRF.
17.	Both the Principal Investigator and the Sponsor must approve patient eligibility prior to randomization. Randomization will be done by using an interactive voice or web-response system (IXRS) on Day 1.
18.	All patients must be vaccinated against N. meningitidis (if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer). Patients must be vaccinated at least 14 days prior to receiving the first IP dose or be vaccinated and receive treatment with appropriate

Footnote	Description
19.	During the Study Period, IP (eculizumab [600 mg, 900 mg or 1200 mg] or matching placebo) will be administered IV over approximately 35 minutes according to the following regimen: **Induction Phase** 3 vials of IP (equivalent to 900 mg of eculizumab) weekly x 4 (every 7 days ±2 days) followed by 4 vials of IP (equivalent to 1200 mg of eculizumab) one week later for the fifth dose (Visit 6). **Maintenance Phase** 4 vials of IP (equivalent to 1200 mg of eculizumab) every two weeks (14 days ±2 days) ***Supplemental Doses** If patient undergoes PE for On-Trial Relapse on a day that IP administration is not routinely scheduled during the Study Period, a supplemental dose (2 vials IP; equivalent to 600 mg of eculizumab) must be administered after each PE, preferably within 1-2 hours. Patients will continue in accordance with the protocol specified IP administration schedule (i.e., if PE is administered on the day of regularly scheduled IP administration, patients will receive the regularly scheduled number of vials [3 vials on Visits 2-5, 4 vials on all other Visits] after each PE, preferably within 1-2 hours).
20.	Patient should be evaluated within 24-48 hours of notification of the Investigator of a potential relapse, and no later than 48 hours. All potential relapses must be evaluated by both the Treating Physician and the blinded EDSS Rater. Follow-Up Relapse Evaluation Visits will be performed at 1, 4 and 6 weeks after the onset of relapse. Additional Relapse Evaluation Visits (Unscheduled Visits) are permitted at the discretion of the Treating Physician. Tests, procedures and assessments listed under the Unscheduled Visits are to be performed at the discretion of the Investigator. All investigations/tests related to the relapse evaluation
Abbreviations	B = Baseline sample; CSF = Cerebrospinal Fluid; EOS = End of Study; ET = Early Termination; HAHA = Human anti-human antibody; T = Trough sample; P = Peak sample; V = Visit; W = Week

13.8. EDSS scale score

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory, and the precise step number is defined by the Functional System (FS) score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation, and usual equivalents in Functional System scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS. Each step (e.g., 3.0 to 3.5) is still part of the DSS scale equivalent (i.e., 3). Progression from 3.0 to 3.5 should be equivalent to the DSS score of 3.

0 - Normal neurological exam (all grade 0 in FS).
1.0 - No disability, minimal signs in one FS (i.e., grade 1).
1.5 - No disability, minimal signs in more than one FS (more than on FS grade 1).
2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).
4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest 500 meters.
4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance: characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions): (usual FS equivalents are one grade 5 alone, others 0 or 1: or combinations of lesser grades usually exceeding specifications for step 4.0).
5.5 - Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities: (usual FS equivalents are one grade 5 alone, others 0 or 1: or combination of lesser grades usually exceeding those for step 4.0).
6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting: (usual FS equivalents are combinations with more than two FS grade 3 +).
6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting (usual FS equivalents are combinations with more than two FS grade 3 +).
7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to a wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (usual FS equivalents are combinations with more than one FS grad 4 +; very rarely pyramidal grade 5 alone).

7.5 - Unable to take more than a few steps; restricted to wheelchair, may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair; (usual FS equivalents are combinations with more than one FS grade 4 +).
8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day, retains many self-care functions; generally has effective use of arms; (usual FS equivalents are combinations, generally grade 4 + in several systems).
8.5 - Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions; (usual FS equivalents are combinations generally 4 + in several systems).
9.0 - Helpless bed patient: can communicate and eat; (usual FS equivalents are combinations, mostly grade 4 +).
9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (usual FS equivalents are combinations, almost all grade 4 +).
10.0 - Death due to MS.

13.9. Optico-spinal Impairment Score (OSIS)

Visual Acuity (VA)

0 Normal
1 Scotoma but VA (corrected) better than 20/30
2 VA 20/30 - 20/59
3 VA 20/60-20/100
4 VA 20/ I 0 I - 201200
5 VA 20/20 I - 20/800
6 Count fingers only
7 Light perception only
8 No light perception

Motor Function

0 Normal

1 Abnormal signs (hyperreflexia, Babinski sign) without weakness
2 Mild weakness (MRC grade 5- or 4+) in affected limb(s)
3 Moderate weakness (grade 3 or 4) in 1 or 2 UMN muscles in affected limb(s)
4 Moderate weakness (grade 3 or 4) in 3 UMN muscles in affected limb(s)
5 Severe weakness (grade 2) in 1 or more muscles in affected limb(s)
6 Some plegic (grade 0 or 1) muscles in 1 or more limbs
7 Plegia (grade 0 or 1) of all muscles in 1 or more limbs

Sensory Function

0 Normal
1 Mild decrease in vibration
2 Mild decrease in pinprick/temperature/proprioception or moderate decrease in vibration
3 Moderate decrease in touch/pin/proprioception or essentially lost vibration sense
4 Loss of all sensory modalities
5 Unknown

Sphincter Function

0 Normal
1 Mild urinary urgency or hesitancy; constipation
2 Moderate urinary urgency, hesitancy, or retention of bladder or bowel, infrequent urinary incontinence (less than once/week)
3 Frequent incontinence or retention requiring intermittent bladder catheterization or aggressive (manual) bowel assistance
4 Indwelling urinary catheter or absence of sphincter control
5 Unknown

13.10. Hauser Ambulation Index

0 = Asymptomatic; fully active.
1 = Walks normally, but reports fatigue that interferes with athletic or other demanding activities.
2 = Abnormal gait or episodic imbalance; gait disorder is noticed by family and friends; able to walk 25 feet (8 meters) in 10 seconds or less.
3 = Walks independently; able to walk 25 feet in 20 seconds or less.
4 = Requires unilateral support (cane or single crutch) to walk; walks 25 feet in 20 seconds or less.
5 = Requires bilateral support (canes, crutches, or walker) and walks 25 feet in 20 seconds or less; or requires unilateral support but needs more than 20 seconds to walk 25 feet.
6 = Requires bilateral support and more than 20 seconds to walk 25 feet; may use wheelchair* on occasion.
7 = Walking limited to several steps with bilateral support; unable to walk 25 feet; may use wheelchair* for most activities.
8 = Restricted to wheelchair; able to transfer self independently.
9 = Restricted to wheelchair; unable to transfer self independently.

*The use of a wheelchair may be determined by lifestyle and motivation. It is expected that patients in Grade 7 will use a wheelchair more frequently than those in Grades 5 or 6. Assignment of a grade in the range of 5 to 7, however, is determined by the patient's ability to walk a given distance, and not by the extent to which the patient uses a wheelchair.

13.11. Modified Rankin Scale score

0 No symptoms at all
1 No significant disability despite symptoms; able to carry out all usual duties and activities
2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3 Moderate disability; requiring some help, but able to walk without assistance

4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6 Dead

TOTAL (0–6

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/s/

LAWRENCE D RODICHOK
06/27/2019 10:26:59 AM

PAUL R LEE
06/27/2019 10:35:28 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166s431

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 #:	BLA 125,166 /Supplement 431
Drug Name:	Eculizumab (Soliris®)
Indication(s):	Neuromyelitis Optica Spectrum Disorder (NMOSD)
Applicant:	Alexion Pharmaceuticals, Inc.
Date(s):	Date of Submission: December 28, 2018 PDUFA Date: June 28, 2019
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Sharon Yan, PhD
Concurring Reviewers:	Kun Jin, PhD, Team Leader Jim Hung, PhD, Director
Medical Division:	Neurology
Clinical Team:	Lawrence Rodichok, MD, Clinical Reviewer Paul Lee, MD, PhD, Clinical Team Leader Nicholas Kozauer, MD, Associate Director Eric Bastings, MD, Deputy Director Billy Dunn, MD, Director
Project Manager:	Nahleen Lopez, PharmD, MS-HCA, RPM

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1 EXECUTIVE SUMMARY

This supplemental BLA application by Alexion is seeking approval of eculizumab for the following indications: ***Soliris® (eculizumab) is indicated for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.***

Alexion's eculizumab clinical development program in NMOSD included one Phase 3 randomized, double-blind, placebo-controlled, multicenter study (Study ECU-NMO-301) and one open-label, extension study of Study ECU-NMO-301 (Study ECU-NMO-302; ongoing).

The pivotal Study ECU-NMO-301 assessed the efficacy of eculizumab, as compared to placebo, based on time to first adjudicated On-trial Relapse and relapse risk reduction. The efficacy outcome of the study included results from 143 adult patients, of whom 96 were treated with eculizumab and 47 were treated with placebo.

Patients who received eculizumab showed a statistically significant effect on time to first adjudicated On-trial Relapse compared with placebo ($p<0.0001$), corresponding to a 94.2% reduction in relapse risk.

2 INTRODUCTION

2.1 Overview

NMOSD is an ultra-rare severe, disabling, autoimmune inflammatory disorder of the central nervous system that predominately affects the optic nerves and spinal cord, and less commonly the brain. Currently, no therapies are approved for the treatment of NMOSD.

The eculizumab NMOSD clinical development program included one randomized, double-blind, placebo-controlled Phase 3 trial (ECU-NMO-301) and one ongoing open-label extension trial (ECU-NMO-302) in patients with NMOSD who were anti-AQP4 antibody positive.

The FDA issued an SPA agreement for the pivotal trial ECU-NMO-301, referred as Study 301 thereafter, on May 1st, 2013, but rescinded the SPA agreement on November 21, 2013. The agreement was rescinded on the basis that a positive outcome in the study might not necessarily be attributed to eculizumab due to the potential background effect of immunosuppressive therapy (IST) and that review of the trial results would be required to determine whether any beneficial treatment effect attributed to eculizumab could be distinguished from the effects of the variety of ISTs given concomitantly with the study drug during the trial.

The following table presents a summary of the study.

Table 1 List of All Studies Included in This Review

Protocol	Phase and Design	Treatment Period	Comparator	# of Subjects per Arm	Study Population
ECU-NMO-301	Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter, time-to-event study; Randomization 2:1 (eculizumab:placebo)	Treatment duration for an individual patient varied in this time-to-event study.	Placebo	143 Randomized (eculizumab: 96 Placebo: 47)	NMOSD patient who were anti-AQP4-Ab positive

Source: Reviewer's summary

2.2 Data Sources

All documents reviewed for this BLA supplement submission are in electronic form. The path to the original submission on 12/28/2018 is \\CDSESUB1\evsprod\BLA125166\0659.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No major issues were identified in the submission of data and study documents.

3.2 Evaluation of Efficacy

3.2.1 Study Design

Study 301 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study. The primary objective of Study 301 was to assess the efficacy and safety of eculizumab, as compared with placebo, in relapsing NMOSD patients based on time to first relapse and relapse risk reduction.

Eligible patients were randomized on Day 1 on a 2:1 ratio to the eculizumab group or the placebo group. The randomization stratification included 2 variables: (1) Expanded Disability Status Scale (EDSS) score at randomization ($\leq$ 2.0 vs. $\geq$ 2.5); and (2) patients' prior immunosuppressive (IST) status at randomization (IST naïve, continuing on the same IST(s) since the last relapse, or with changes in IST(s) since the last relapse).

Patients could continue to receive a stable dose of the IST they were taking at the time of screening, but no new ISTs and no change in IST dosage were permitted during the study except for a known toxicity or side effect associated with the given IST.

Patients completed the study if they experienced an On-trial Relapse per the Treating Physician or once the prespecified number of patients had experienced a positively-adjudicated On-trial Relapse, whichever occurred first. The 24th adjudicated On-trial Relapse was planned to trigger end of study (EOS) activities. For patients who had On-Trial relapse, the Week 6 Post-Relapse Evaluation Visit also served as the EOS Visit for these patients.

In May 2018, Alexion ended the study at 23 adjudicated On-trial Relapses. This action was taken following a review of blinded data, which Alexion concluded that terminating the study at 23 adjudicated events (i.e., 96% complete) had low risk of impacting the study outcome.

The NMOSD patient population in Study 301 consisted of patients who were anti-AQP4-Ab positive and who had experienced at least 2 relapses in the 12 months prior to Screening or 3 relapses in the 24 months prior to Screening (with at least 1 relapse in the 12 months prior to Screening).

3.2.2 Study Endpoints

The primary endpoint of the study was time to first adjudicated On-trial Relapse.

The definitions of On-trial Relapse and adjudicated On-trial Relapse were as follows:

On-trial Relapse: an On-trial Relapse is a relapse that occurs during the Study Period, defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (clinical sign) on neurologic examination that persists for more than 24 hours as confirmed by the Treating Physician.

Adjudicated On-trial Relapse (primary endpoint): an adjudicated On-trial Relapse is defined as an On-trial Relapse that is positively adjudicated by the Relapse Adjudication Committee (RAC).

Secondary efficacy endpoints were rank ordered as follows:

1. Adjudicated On-Trial annualized relapse rate (ARR)
2. Change from baseline in EDSS score at the EOS
3. Change from baseline in mRS score at the EOS
4. Change from baseline in ambulatory function as measured by HAI at the EOS
5. Change from baseline in EQ-5D at the EOS

3.2.3 Statistical Methodologies

3.2.3.1 General Consideration

All efficacy analyses were to be performed based on Fall Analysis Set (FAS), which consisted of all patients who were randomized and who had received at least 1 dose of study drug.

Since small numbers of patients were expected in some cells of the strata, it was planned to collapse the 6 randomized strata into 4 strata: (1) low EDSS stratum at randomization (≤ 2.0), (2) high EDSS stratum (≥2.5 to ≤ 7) and treatment naïve patients at randomization, (3) high EDSS stratum (≥2.5 to ≤ 7) and patients continuing on the same IST(s) since last relapse at randomization, and (4) high EDSS stratum (≥2.5 to ≤ 7) and patients with changes in IST(s) since last relapse at randomization.

3.2.3.2 Analyses of the Primary Endpoints

The comparison of the treatment groups for the primary endpoint of time to first adjudicated On-Trial Relapse was to use a log-rank test including strata for the randomization stratification variable. Hazard ratio and risk reduction from a stratified Cox proportional hazards model were to be summarized. A sensitivity analysis was to be performed on time to first On-Trial Relapse as determined by the Treating Physician using the same stratified log-rank test.

3.2.3.3 Analysis of Secondary Endpoints

Hypothesis testing comparing eculizumab with placebo for secondary efficacy endpoints was to be performed using a closed testing procedure with the following rank order:

1. Adjudicated On-Trial annualized relapse rate (ARR)
2. Change from baseline in EDSS score at the EOS
3. Change from baseline in mRS score at the EOS
4. Change from baseline in ambulatory function as measured by HAI at the EOS
5. Change from baseline in EQ-5D at the EOS

The EQ-5D consisted of two endpoints, the EQ-5D Index score and EQ-5D VAS. For the purposes of this closed testing procedure, the EQ-5D VAS score was the first and the EQ-5D Index score was the second to be tested.

Adjudicated On-Trial ARR was to be analyzed using a Poisson regression analysis with treatment group, the randomization stratification variable, and historical annualized relapse rate as covariates, with the log of time in the study as the offset variable.

A sensitivity analysis was to be performed for ARR using all On-Trial Relapses using the same Poisson regression analysis as in the ARR for On-Trial Adjudicated Relapses.

The primary analysis for the change from baseline in EDSS scores to the EOS (i.e. 6 week post-relapse for patients who had relapses or EOS for patients who did not have relapses) was a randomization-based nonparametric ANCOVA adjusted for baseline EDSS and stratified by randomization IST strata. A sensitivity analysis for the change from baseline in EDSS score to the EOS was an ANCOVA with treatment group, baseline EDSS, and randomization IST strata as covariates.

Changes from baseline to EOS in mRS, HAI, EQ-5D VAS, and EQ-5D index score were to be analyzed in a similar manner as changes in EDSS score.

3.2.3.4 Handling of Missing Values

Patients who did not have adjudicated On-Trial Relapses were to be censored at the EOS in the primary analysis.

Missing data for the primary analysis of EDSS, mRS, HAI, and EQ-5D at the EOS were to be handled as follows: If the assessment 6 weeks after the first relapse was missing or if a non-relapse patient was missing the EOS score, the last observed score from a protocol scheduled visit was to be used. If a patient had no post-baseline assessments, the baseline value was to be used. If a patient experienced a second relapse during the 6-week recovery phase after the initial relapse, the last score prior to the second attack was to be used for the analysis.

3.2.4 Study Results

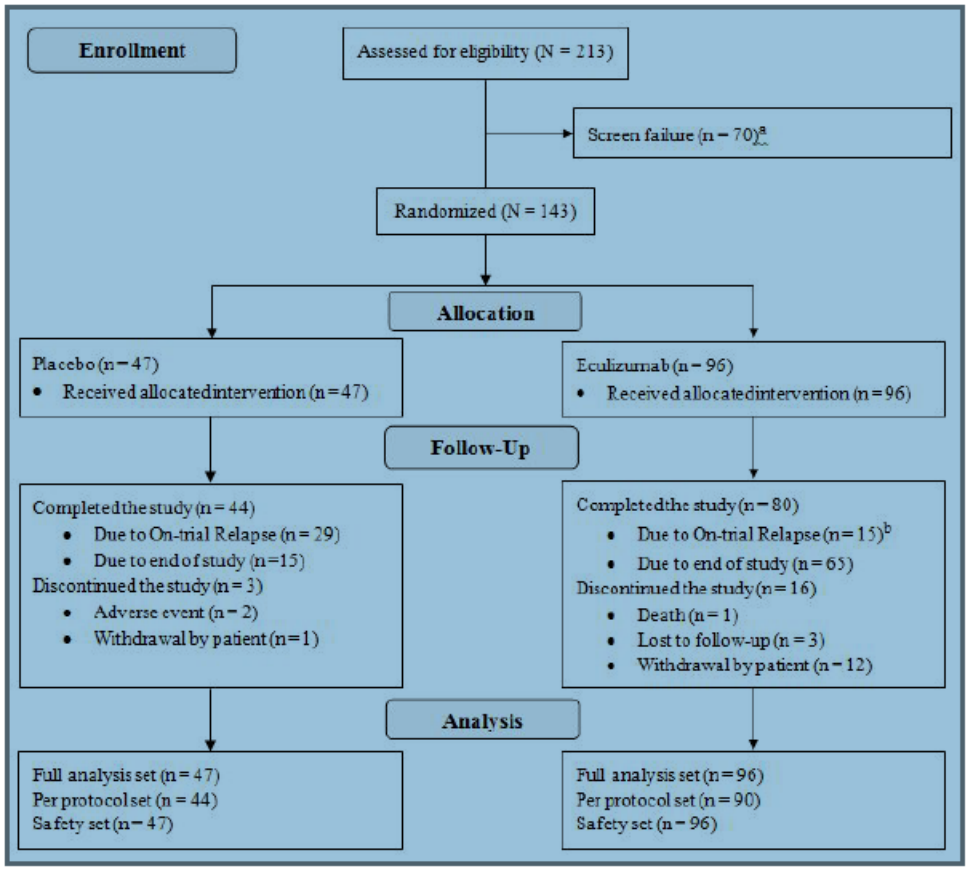
3.2.4.1 Patient Disposition

A total of 213 patients were screened, of which 143 patients were randomized (96 patients randomized to the eculizumab group and 47 patients randomized to the placebo group).

Of the 143 total patients treated in the study, 124 (86.7%) patients completed the study and 19 (13.3%) patients discontinued from the study (16 [16.7%] patients in the eculizumab group and 3 [6.4%] patients in the placebo group).

Among the 16 patients discontinued study in the eculizumab group, 4 patients discontinued within 6 months (ranged 31 to 86 days), 6 patients discontinued between 6 to 12 months (ranged 246 to 332 days), and 6 patients discontinued after Day 597. Among the 3 placebo-treated patients discontinued study, 2 patients discontinued due to AD on days 129 and 379, and 1 patient withdrew on Day 351.

The disposition and follow-up of all randomized patients is summarized in Figure 1.



[a] Reasons for screen failure include AQP4-Ab seronegative (n = 42); not having ≥ 2 relapses in the last 12 months or 3 relapses in the last 24 months with at least 1 in the 12 months prior (n = 11); EDSS score > 7 (n = 5); Investigator decision (n = 5); daily corticosteroid dose more than prednisone 20 mg/day (or equivalent) after Screening (n = 3); patient not willing or able to comply with the protocol requirements (n = 3); and patient did not give written informed consent (n = 2).

[b] This includes 1 patient who experienced a relapse that was outside of the analysis window defined for an "On-trial Relapse" (Section 9.5.1.1); thus, this relapse is not considered an On-trial Relapse in the efficacy analyses

Abbreviations: AQP4-Ab = aquaporin 4 antibody; EDSS = Expanded Disability Status Scale.

Figure 1 Diagram of Patient Disposition and Follow-up

Source: Figure 1 of Clinical Study Report

3.2.4.1.1 Patient Demographics

Overall, the demographics of patients were similar in the 2 treatment groups. The majority (90.9%) of patients overall were female, 49% of the patients were White and 36.4% were Asian.

Table 2 Demographic Characteristics (Randomized Subjects)

Variable	Statistic	Placebo N=47	Eculizumab N=96
Age at first Dose (years)	Mean (SD) Median	45.0 (13.29) 44.0	43.9 (13.32) 45.0
Sex			
Male	n (%)	5 (10.6)	8 (8.3)
Female	n (%)	42 (89.4)	88 (91.7)

Ethnicity			
Hispanic or Latino	n (%)	3 (6.4)	13 (13.5)
Not Hispanic or Latino	n (%)	41 (87.2)	78 (81.3)
Not reported or unknown	n (%)	3 (6.4)	5 (5.2)
Region			
Americas	n (%)	15 (31.9)	29 (30.2)
Europe	n (%)	19 (40.4)	32 (33.3)
Asia Pacific	n (%)	13 (27.7)	35 (36.5)

Source: Table 17 of Clinical study Report

3.2.4.1.2 Patient Baseline Disease Characteristics and IST Status

Patient baseline disease characteristics and IST status were balanced between the two treatment groups. The majority of patients in both treatment groups were in the high EDSS (≥ 2.5 to ≤ 7) strata, either continuing on the same IST(s) since their last relapse or changes in the IST(s) at last relapse prior to randomization.

Table 3 Baseline Disease Characteristics and Status of IST Treatment – Full Analysis Set

Variable	Statistic	Placebo N=47	Eculizumab N=96
Prior 24-month ARR	Mean (SD)	2.1 (1.04)	1.9 (0.90)
	Median	1.9	1.9
Baseline EDSS Score	Mean (SD)	4.3 (1.51)	4.2 (4.0)
	Median	4.0	4.0
Randomization Strata			
EDSS $\leq$ 2.0	n (%)	5 (10.6)	11 (11.5)
2.5 $\leq$ EDSS $\leq$ 7, IST Naive	n (%)	5 (10.6)	12 (12.5)
2.5 $\leq$ EDSS $\leq$ 7, same IST since last relapse	n (%)	22 (46.8)	44 (45.8)
2.5 $\leq$ EDSS $\leq$ 7, change in IST since last relapse	n (%)	15 (31.9)	29 (30.2)
HAI Score	Mean (SD)	2.1 (1.40)	2.4 (2.17)
	Median	2.0	2.0
mRS Score	Mean (SD)	2.1 (0.98)	2.1 (1.14)
	Median	2.0	2.0
Observed IST Stratification[1]			
IST naïve at randomization	n (%)	5 (10.6)	14 (14.6)
Same IST since last relapse at randomization	n (%)	24 (51.1)	49 (51.0)
Changed IST since last relapse at randomization	n (%)	18 (38.3)	33 (34.4)

1. The IST randomization stratification is somewhat different from the IST observed stratification.

Source: Tables 20 and 21 of Clinical Report and reviewer's summary

3.2.4.2 Efficacy Results

It was planned that the study was to end when 24 adjudicated On-Trial relapses were reached. On 17 May 2018, Alexion ended the study at 23 adjudicated On-trial Relapses. The program DMC and Health Authorities, including FDA, EU competent authorities, and PMDA, were informed of this decision. It was stated that the early termination of the study was not driven by safety or efficacy concerns.

3.2.4.2.1 Primary Endpoint – Time to First Adjudicated On-Trial Relapse

In the FAS, 3 (3.1%) patients in the eculizumab group and 20 (42.6%) patients in the placebo group had an adjudicated On-trial Relapse. A statistically significant effect on the time to first adjudicated On-trial Relapse was observed for eculizumab compared with placebo (p<0.0001). The hazard ratio for eculizumab compared with placebo was 0.058, representing a 94.2% reduction in the risk of relapse. Table 4 presents a summary of the results from analysis of the primary endpoint.

Table 4 Analysis of Time to First Adjudicated On-Trial Relapse

Variable	Statistic	Placebo N=47	Eculizumab N=96
Patients with Adjudicated Relapse	n (%)	20 (42.6)	3 (3.1)
Time to 1st Adjudicated Relapse **Treatment effect** – log-rank test	p-value		< 0.0001
Secondary test – Cox model	Hazard ratio (HR) 95 C.I. of HR % of reduction p-value		0.058 (0.017, 0.197) 94.2 <0.0001
Sensitivity Analysis Time to first On-trial Relapse Patient with on-trial relapse Log-rank test Cox model	 n (%) p-value p-value Hazard ratio (HR) 95 C.I. of HR % of reduction	 29 (61.7)	 14 (14.6) < 0.0001 <0.0001 0.180 (0.095, 0.343) 82.0

Source: Table 24 of the Clinical Study Report, results verified by reviewer.

Kaplan=Meier estimate for time to first Adjudicated On-Trial Relapse is presented in Figure 2.

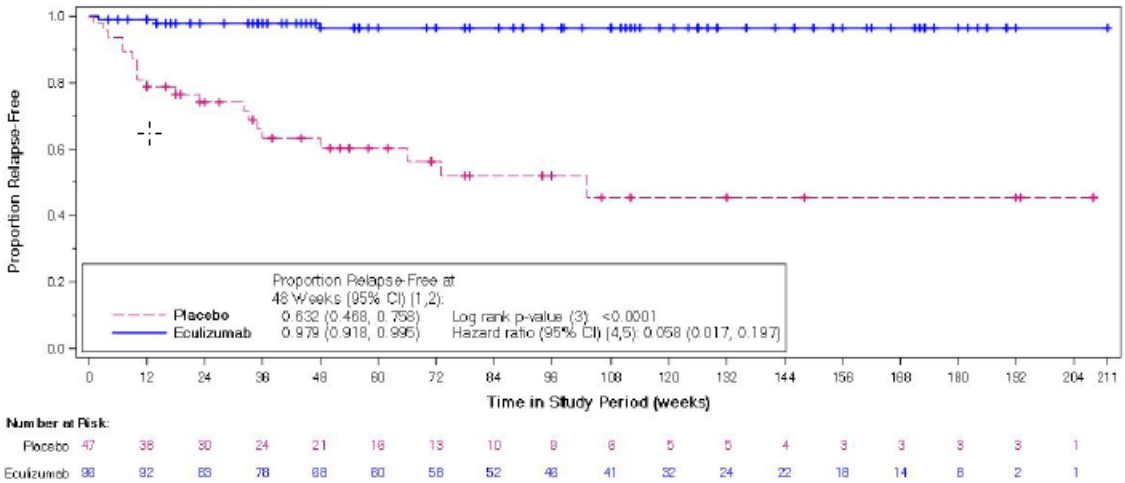


Figure 2 Kaplan-Meier Estimated for Time to First Adjudicated On-trial Relapse
Source: Figure 2 of the Clinical Study Report

3.2.4.2.2 Secondary Endpoints

Annualized Relapse Rate

A total of 45 On-Trial relapses occurred; 31 in the placebo group and 14 in the Eculizumab. Among those On-Trial relapses, 24 were adjudicated; 21 in the placebo group and 3 in the eculizumab. One patient in the placebo group had 2 adjudicated relapses, compared to none in the Eculizumab group. Note that this study was not designed to observe more than one On-Trial relapse since patients who experienced an On-trial Relapse were to discontinue from the trial after completing the Week 6 Post-Relapse Evaluation Visit. The adjusted adjudicated On-trial ARRs in the placebo group and the eculizumab group were 0.350 and 0.016, respectively. The rate ratio of eculizumab over placebo was 0.045, representing a 95.5% reduction in adjudicated On-trial ARR for patients treated with eculizumab compared with placebo. The results of Adjudicated ARR and On-trial ARR are summarized in Table 5.

Table 5 Annualized Relapse Rate

Variable	**Statistic**	**Placebo N=47**	**Eculizumab N=96**
Number of Adjudicated Relapses	Total	21	3
Patients with 0 adjudicated relapse	n (%)	27 (57.5)	93 (96.9)
Patients with 1 adjudicated relapse	n (%)	19 (40.4)	3 (3.1)
Patients with 2 adjudicated relapses	n (%)	1 (2.1)	0
Adjusted Adjudicated ARR	Rate	0.350	0.016
	95% CI	(0.199, 0.616)	(0.005, 0.050)
	Rate ratio		0.045
	95% CI of the ratio		(0.013, 0.151)
	p-value		<0.0001
Number of On-Trial Relapses	Total	31	14
Patients with 0 relapse	n (%)	18 (38.3)	82 (85.4)
Patients with 1 relapse	n (%)	27 (57.5)	14 (14.6)
Patients with 2 relapses	n (%)	2 (4.3)	0
Adjusted On-Trial ARR	Rate	0.446	0.066
	95% CI	(0.272, 0.732)	(0.036, 0.120)
	Rate ratio		0.147
	95% CI of the ratio		(0.078, 0.278)
	p-value		<0.0001

Source: Reviewer's analysis

Change from Baseline in EDSS at the End of the Study

The primary analysis for change from baseline in EDSS was originally a rank based ANCOVA. In the last version of SAP (Version 5, finalized June 1, 2018, not previously submitted to the Division), the analysis was changed to a randomization based non-parametric ANCOVA proposed in Koch, et al (Koch 1998), with generic SAS code using a SAS/IML (interactive macro language) macro call.

Since the methodology and SAS codes for the analysis was not reviewed by the Agency and the SAP was not submitted prior to the BLA submission, the original rank based ANCOVA was considered as the primary analysis in this review.

The median change from Baseline in EDSS score at the End of Study (EOS) was 0.00 for both treatment groups. The distribution for the change from baseline to EOS in EDSS score showed 51.0% of the eculizumab-treated patients and 42.6% of the placebo-treated patients had no change, 29.2% of the eculizumab-treated patients and 29.8% of the placebo-treated patients had a ≥ 0.5 point improvement, while 19.8% of the eculizumab-treated patients and 27.7% of the placebo-treated patients had a ≥ 0.5 point worsening in EDSS score.

The sponsor reported a non-significant treatment difference with a p-value of 0.0597 from a randomization based non-parametric ANCOVA proposed in Koch, et al (Koch 1998). As stated above, the rank based ANCOVA analysis was considered as a primary analysis in this review. The rank based ANCOVA yielded a p-value of 0.4464 for the treatment difference.

Other sensitivity analyses reported by the sponsor included ANCOVA analysis without rank transformation (p=0.0603) and MMRM analysis (p=0.4855). None of these analyses indicated there was a statistically significant treatment difference in the change from baseline of EDSS scores.

Table 6 Change from Baseline to End of Study in EDSS Score

Variable	**Statistic**	**Placebo N=47**	**Eculizumab N=96**
Baseline EDSS Score	Mean (SD) Median	4.26 (1.51) 4.0	4.15 (1.65) 4.0
Change in EDSS No change Increase (worsening) Decrease (improvement)	Mean (SD) Median n (%) n (%) n (%)	0.12 (0.95) 0 20 (42.6%) 13 (27.7%) 14 (29.8%)	-0.18 (0.81) 0 49 (51.0%) 19 (19.8%) 13 (13.5%)
Primary Analysis: Rank ANCOVA	p-value		0.4464
Sponsor: Randomization Based Non-parametric ANCOVA	p-value		0.0597
Sensitivity Analysis ANCOVA on original score	LS mean (SE) p-value	0.03 (0.133)	-0.26 (0.096) 0.0603
Sensitivity Analysis MMRM	LS mean (SE) p-value	-0.30 (0.101)	-0.38 (0.070) 0.4855

Source: Clinical Study Report and Reviewer's analysis

Change from Baseline in mRS at the End of the Study

The hierarchical testing for inferential analysis was stopped due to the insignificant treatment difference in EDSS results. The results from analysis of mRS is presented for descriptive purpose only.

The median change from Baseline in mRS score at End of Study was 0.00 in both treatment groups. The majority of the patients (67.7% of the eculizumab-treated patients and 74.5% of the placebo-treated patients) had no change, 26.0% of the eculizumab-treated patients and 10.6% of the placebo-treated patients had a ≥ 1 point improvement in mRS score, while 6.3% of the eculizumab-treated patients and 14.9% of the placebo-treated patients had a ≥ 1 point worsening in mRS score. The results are presented in Table 7.

Table 7 Change from Baseline to End of Study in mRS Score

Variable	Statistic	Placebo N=47	Eculizumab N=96
Baseline mRS Score	Mean (SD) Median	2.15 (0.98) 2.0	2.15 (1.14) 2.0
Change in mRS	Mean (SD) Median	0.09 (0.75) 0	-0.24 (0.72) 0
No change Increase (worsening) Decrease (improvement)	n (%) n (%) n (%)	35 (74.5%) 7 (14.9%) 5 (10.6%)	65 (67.7) 6 (6.3%) 25 (26.0%)
Primary Analysis: Rank ANCOVA	Nominal p-value		0.0135
Sensitivity Analysis ANCOVA on original score	LS mean (SE) Nominal p-value	0.00 (0.115)	-0.32 (0.084) 0.0154
Sensitivity Analysis MMRM	N LS mean (SE) Nominal p-value	42 -0.19 (0.082)	93 -0.30 (0.056) 0.2459

Source: Reviewer's analysis

The meaningfulness of secondary endpoints in the form of change from baseline to end of study is questionable. The treatment period for this study varied by patients and the duration of the whole trial, from enrollment of the first patient to the end of the study, lasted more than 4 years. At the end of the study when 23 adjudicated relapses were reached, the first enrolled patient had been in study for 4 years, while the last enrolled patient had been treated for less than 6 months. The number of patients at each scheduled assessment reduced substantially toward the end of the study due to 1) patients who had a relapse exited the study; or 2) patients who was enrolled in the late stage of the study reached end of the study before scheduled assessments. In addition, the placebo group had more patients who had relapses and Eculizumab group had more patient who dropped out of the study. Therefore, the mean change from baseline was based on an increasingly smaller patient population, who was likely having different profile from the ITT population. The following table presents the mean change from baseline in mRS by visit with the number of patients available for the analysis.

Table 8 Change from Baseline in mRS by Visit

	Placebo N=47		Eculizumab N=96	
	n	Mean	n	Mean
Baseline	47	2.15	96	2.15
Week 4	43	0.16	92	-0.03
Week 8	41	0.05	89	-0.09

Week 24	28	-0.04	82	-0.18
Week 36	24	-0.08	76	-0.28
Week 48	20	0.0	65	-0.20
Week 60	14	0.0	59	-0.19
Week 72	12	0.0	57	-0.25
Week 84	10	-0.10	51	-0.18
Week 96	8	-0.13	43	-0.23

Source: Reviewer's summary

The same concern pointed out above applies to the results of all secondary endpoints with the form of change from baseline.

Change from Baseline in Hauser Ambulation Index Score at End of Study

The hierarchical testing for inferential analysis was stopped due to the insignificant treatment difference in EDSS results. The results from analysis of HAI score are presented for descriptive purpose only.

The median change from Baseline in HAI score at End of Study was 0.0 in both treatment groups. The distribution for the change from Baseline to End of Study in HAI score showed 52.1% of the eculizumab-treated patients and 66.0% of the placebo-treated patients had no change, 38.5% of the eculizumab-treated patients and 10.6% of the placebo-treated patients had a ≥ 1-point improvement in HAI score, while 9.4% of the eculizumab-treated patients and 23.4% of the placebo-treated patients had a ≥ 1-point worsening in HAI score.

Table 9 Change from Baseline in Hauser Ambulation Index Score at End of Study

Variable	Statistic	Placebo N=47	Eculizumab N=96
Baseline HAI Score	Mean (SD) Median	2.15 (1.40) 2.0	2.38 (2.17) 2.0
Change in HAI score	Mean (SD) Median	0.51 (1.61) 0	-0.39 (1.08) 0
No change Increase (worsening) Decrease (improvement)	n (%) n (%) n (%)	31 (66.0%) 11 (23.4%) 5 (10.6%)	50 (52.1%) 9 (9.4%) 37 (38.5%)
Primary Analysis: Rank ANCOVA	Nominal p-value		0.0001
Sensitivity Analysis ANCOVA on original score	LS mean (SE) Nominal p-value	0.37 (0.201)	-0.50 (0.147) 0.0002
Sensitivity Analysis MMRM	N LS mean (SE) Nominal p-value	42 -0.26 (0.114)	93 -0.46 (0.079) 0.1021

Source: Reviewer's analysis

Change from Baseline in EQ-5D Scores at End of Study

For the same reason as for other secondary endpoints, the results from analysis of EQ-5D scores are presented in Table 10 for descriptive purpose only.

Table 10 Change from Baseline in EQ-5D Score at End of Study

Variable	Statistic	Placebo N=47	Eculizumab N=96
Baseline EQ-5D VAS Score	Mean (SD) Median	59.09 (20.39) 60.0	63.6 (20.00) 70.0
Change in EQ-5D VAS Score	Mean (SD) Median	0.57 (10.39) 0.0	5.42 (18.53) 0.0
Primary: Rank ANCOVA for VAS	Nominal p-value		0.1121
Sensitivity Analysis ANCOVA on original score	LS mean (SE) Nominal p-value	1.33 (2.57)	7.76 (1.89) 0.0302
Baseline EQ-5D Index Score	Mean (SD) Median	0.68 (0.20) 0.71	0.68 (0.20) 0.76
Change in EQ-5D Index Score	Mean (SD) Median	-0.04 (0.21) 0.00	0.05 (0.18) 0.03
Primary: Rank ANCOVA for Index	Nominal p-value		0.0021
Sensitivity Analysis ANCOVA on original score	LS mean (SE) Nominal p-value	-0.03	0.06 (0.02) 0.0075

Source: Reviewer's analysis

3.3 Evaluation of Safety

Please refer to Evaluation of Safety by Dr. Lawrence Rodichok.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Only 3 on-trial adjudicated relapses occurred in the eculizumab treatment group. This number of on-trial adjudicated relapses in eculizumab group was too small to be split into subgroup populations to allow a meaningful differentiation of treatment effect in subpopulations. Therefore, no statistical analyses were performed for the treatment difference in subgroup populations in Gender, Race, Age or Region.

4.2 Other Special/Subgroup Populations

It was concerned during the trial that the potential background effect of immunosuppressive therapy (IST) could be confounded with the effect of eculizumab. The following table provides a summary of occurrence of relapses in each IST stratum by treatment groups.

Table 11 Summary of Adjudicated On-trial Relapses by IST Status

	Placebo N=47		Eculizumab N=96	
	n	Number (%) with relapse	n	Number (%) with relapse
IST Naïve	5	2 (40.0%)	14	0
Continue on the same IST since last relapse	24	10 (41.7%)	49	2 (4.1%)
Change in IST since last relapse	18	8 (44.4%)	33	1 (3.0%)

Source: Reviewer's summary

Since all 3 eculizumab-treated patients who had an Adjudicated Relapse were taking IST, the data does not suggest that efficacy of eculizumab was partly due to the effect of IST.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No significant statistical issues were found to be deemed as having significant impact on the efficacy results.

5.2 Collective Evidence

Study 301 has demonstrated that eculizumab is efficacious in delaying relapses and reducing the relapse rate. (b) (4)

5.3 Conclusions and Recommendations

Study 301 has provided sufficient evidence that eculizumab is effective as compared to placebo in delaying/reducing relapses in patients with NMSOD.

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/s/

XIAORONG YAN
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KUN JIN
06/12/2019 11:01:20 AM
I concur with the review.

HSIEN MING J HUNG
06/12/2019 11:36:06 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166s431

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	125166
Link to EDR	\\CDSESUB1\evsprod\BLA125166\0659
Submission Date	12/28/18
Submission Type	Efficacy supplement S-431
Brand Name	Soliris
Generic Name	Eculizumab
Dosage Form and Strength	Injection, solution, 5mg/mL
Route of Administration	Intravenous
Proposed Indication	For the treatment of (b) (4) Neuromyelitis Optica Spec (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.
Applicant	Alexion Pharmaceuticals, Inc
Associated IND	IND 116207
OCP Review Team	Atul Bhattaram, Angela Men
OCP Final Signatory	Angela Men

Contents

1. EXECUTIVE SUMMARY

In this supplemental NDA, the applicant is seeking approval for eculizumab to treat patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.

Eculizumab is currently indicated to treat patients with paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS) and refractory generalized myasthenia gravis (gMG). The approved dosing regimen for gMG indication was evaluated in patients with NMOSD. The dosing regimen being sought for approval is:

- 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.

The sponsor submitted population pharmacokinetic analyses to update the estimated half-life and to evaluate the presented anti-drug antibodies (ADA) information. The primary focus of this review is the evaluation of the proposed labeling changes.

1.1 Recommendations

The proposed labeling changes to Sections 6.2 (Immunogenicity), Section 12.2 (Pharmacodynamics) are acceptable. Minor revision to Section 12.3 (Pharmacokinetics) is proposed.

2. PROPOSED LABELING CHANGES

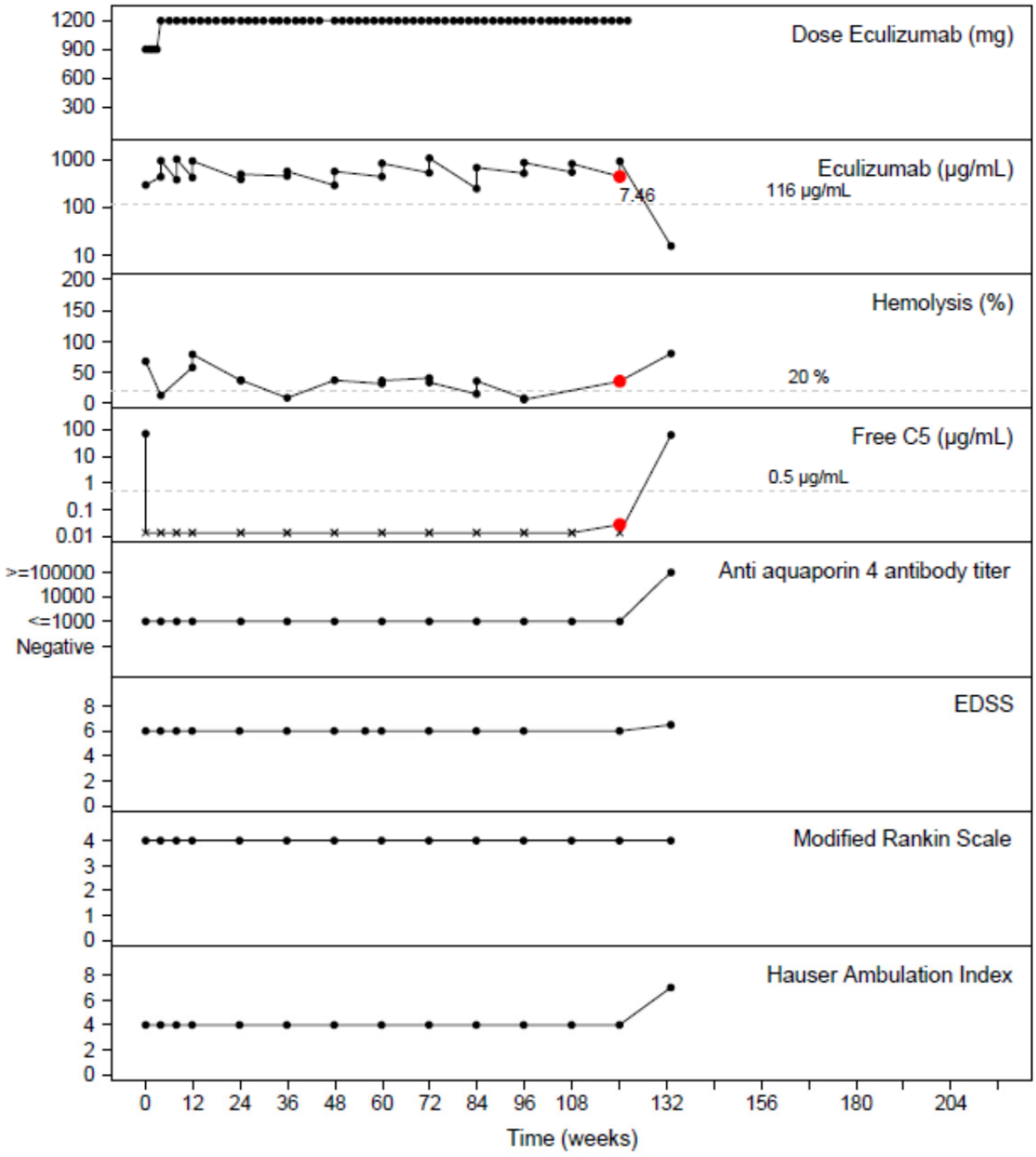
Section 6.2 (Immunogenicity)

Applicant's proposal	Reviewer's findings
The 2/96 of the Soliris-treated patients with NMOSD had antibody to Soliris detected during the entire treatment period. …. none of the 96 patients with NMOSD had low positive values for neutralizing antibodies	The proposed labeling language is acceptable.

Supportive information:

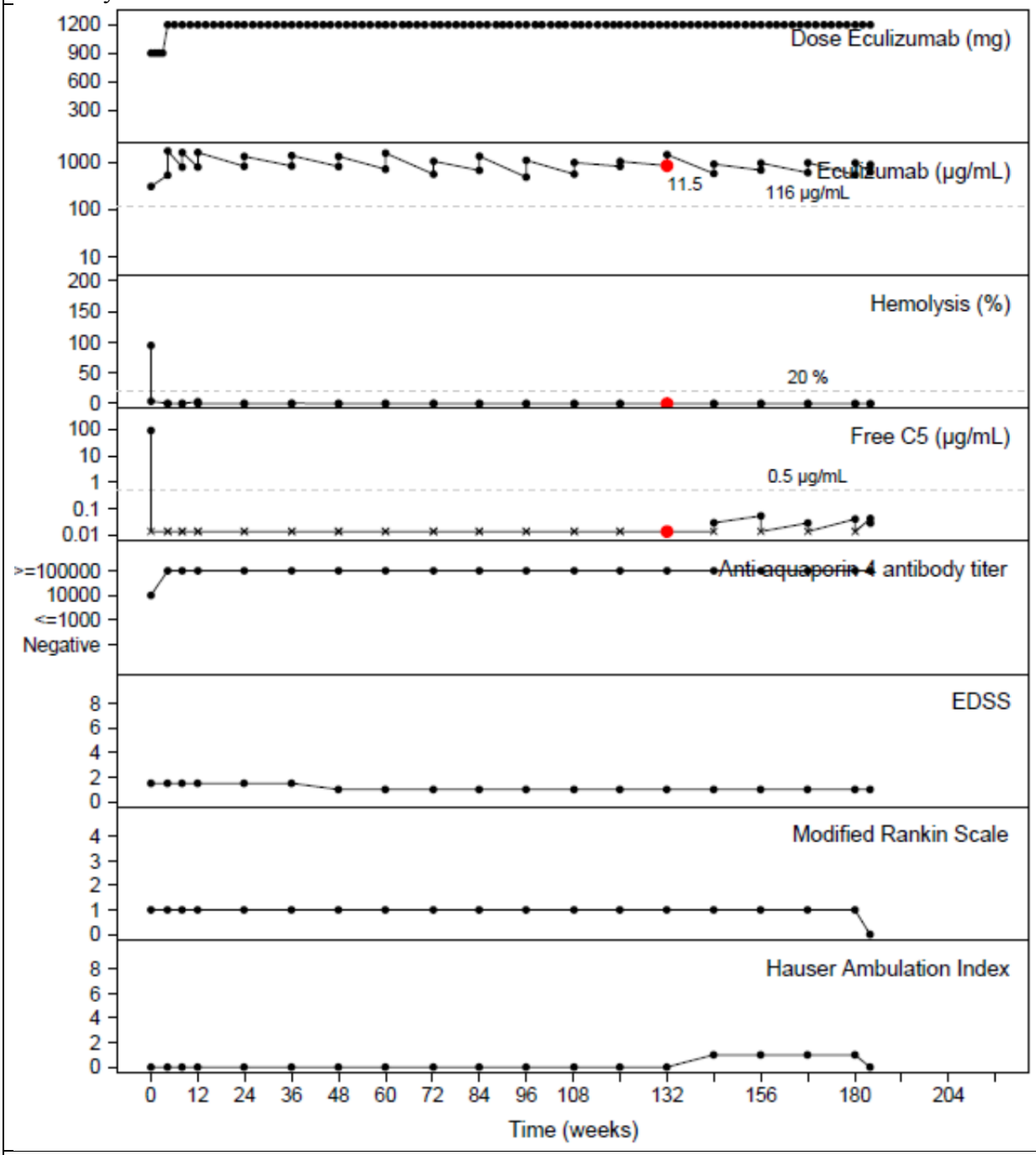
Figure 1 and Figure 2 show the time course of eculizumab concentrations and biomarker/clinical data in 2 patients identified as having anti-drug antibodies. The reviewer from Office of Biotechnology Products noted, these assays are appropriately validated, but relatively insensitive due to background interference of eculizumab in samples. The data from these two patients show no effect of anti-drug antibodies, which are transient, on eculizumab concentrations and other measures of clinical progression (Expanded Disability Status Scale (EDSS) and Modified Rankin scale). Also, the applicant reported that there are no patients with low positive values for neutralizing antibodies.

Figure 1. Eculizumab Dose, Concentrations, Changes in Biomarkers and Clinical Scales in a Patient with Anti-Drug Antibody. Shown in red (•) dot is the Study Visit when Anti-Drug Antibody was Detected.



Source: Page 213 in pop-pk report.pdf

Figure 2. Eculizumab Dose, Concentrations, Changes in Biomarkers and Clinical Scales in a Patient with Anti-Drug Antibody. Shown in red (•) dot is the Study Visit when Anti-Drug Antibody was Detected.



Source: Page 191 in pop-pk report.pdf

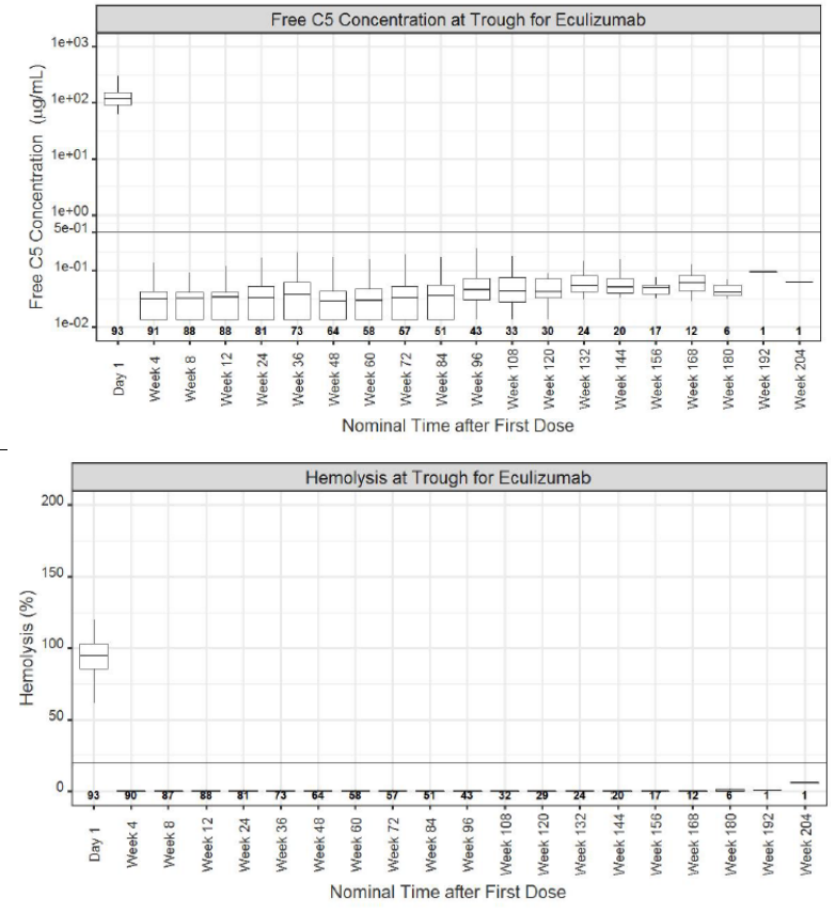
Section 12.2 (Pharmacodynamics)

Applicant's proposal	Reviewer's findings
In patients with PNH, aHUS, gMG, and NMOSD, free C5 concentrations of < 0.5 mcg/mL was correlated with complete blockade of terminal complement activity.	The proposed labeling language is acceptable. Similar information is already mentioned in the label for PNH, aHUS and gMG indications.

Supportive information

Median serum free C5 concentration following the first dose of eculizumab was maintained at < 0.5 µg/mL, the threshold value that is predicted to produce 20% cRBC hemolysis, indicating that immediate, complete, and sustained terminal complement inhibition was achieved.

Figure 3. (Top) Serum Free C5 Concentrations at Eculizumab Trough and (Bottom) Percentage Chicken Red Blood Cell Hemolysis with reference line at 20% at Eculizumab Trough Versus Time Profiles From Study ECU-NMO-301



Source: Figure 2 on page 22 and Figure 3 on page 24 in summary-clin-pharm.pdf

Section 12.3 (Pharmacokinetics)

Applicant's proposal	Reviewer's findings
Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with NMOSD, at week [redacted] the observed mean ± SD C_{max} ranged from 850 ± [redacted] and the C_{trough} [redacted] mcg/mL.	Alternate language is being proposed to be consistent with similar information provided in the current label for PNH, aHUS and gMG indications. For the approved indications, summary measures of C_{max} and C_{trough} at Week 26 are included. In the NMSOD indication, similar information is available at Week 24. To be consistent, the proposed summary measures of C_{max} and C_{trough} values are being revised. *Proposed language:* Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with NMOSD, at week 24, the observed mean ± SD C_{max} was 887±3 [redacted] and the C_{trough} was 4 [redacted]±1 [redacted] mcg/mL.
Elimination The half-life of eculizumab was approximately 270 h to 414 [redacted]	The applicant's population PK analysis is acceptable. The PK model developed for gMG indication was used to analyze the current data. The model diagnostics suggest that the data is well described by the model. The estimate of half-life is 414h and can be included in the label. The estimate of eculizumab half-life is similar across indications.

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/s/

VENKATESH A BHATTARAM
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05/28/2019 10:41:31 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166s431

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 21, 2019

To: Christopher D. Breder, M.D.
Division of Neurology Products (DNP)

Nahleen Lopez, Regulatory Project Manager, DNP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Samuel Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for SOLIRIS (eculizumab) injection for intravenous use

BLA: 125166/S-431

In response to DNP's consult request dated January 11, 2019, OPDP has reviewed the proposed product labeling (PI) for Soliris (eculizumab) injection for intravenous use. This supplement (S-431) provides for a new indication, the treatment of Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients (b) (4) anti-aquaporin-4 (AQP4) antibodies.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP on June 7, 2019 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide was sent under a separate cover on June 14, 2019.

Thank you for your consult. If you have any questions, please contact Koung Lee at (240) 402-8686 or Koung.lee@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 13, 2019
To:	Billy Dunn, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Koung Lee, RPh, MS 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-431
Applicant:	Alexion Pharmaceuticals, Inc.

1 INTRODUCTION

On December 28, 2018, Alexion Pharmaceuticals, Inc. submitted for the Agency's review a Supplemental Biologic License Application (sBLA) for use of SOLIRIS (eculizumab) in the treatment of (b) (4) Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti (AQP4) antibody-positive. Development of eculizumab in the treatment of NMOSD has been carried out under IND 116207.

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 January 14, 2019 and June 7, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SOLIRIS (eculizumab) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft SOLIRIS (eculizumab) MG received on December 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on June 7, 2019.
- Draft SOLIRIS (eculizumab) MG received on December 28, 2018, revised by the Review Division throughout the review cycle, and received by OPDP on June 7, 2019.
- Draft SOLIRIS (eculizumab) Prescribing Information (PI) received on December 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on June 7, 2019.
- Draft SOLIRIS (eculizumab) Prescribing Information (PI) received on December 28, 2018, revised by the Review Division throughout the review cycle, and received by OPDP on June 7, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level

Additionally, 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.

In our collaborative review of the MG we:

- 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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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166s431

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-431
OSE RCM #	2019-773
Reviewer(s)	Bob Pratt, Pharm.D.
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	June 25, 2019
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 neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 antibody-positive

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-431, submitted on December 28, 2018. The REMS for eculizumab was originally approved on June 4, 2010 to mitigate the risk of meningococcal infection and hemolysis post-discontinuation in the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH). The REMS has been modified eight times since approval and consists of elements to assure safe use and a timetable for submission of assessments. The most recent REMS modification was approved July 25, 2018. The Applicant submitted the current proposed REMS modification as part of a supplemental application for a new indication for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in (b) (4) who are anti-aquaporin-4 antibody-positive.

The proposed modification consists of changes to the Prescriber Safety Brochure to add the NMOSD indication statement and to change the word order of the myasthenia gravis indication statement. Otherwise, the REMS document and materials do not require changes, as the REMS-related risks of treatment for the new indication are unchanged compared with the approved indications. The Applicant did not propose any changes to the REMS assessment plan but updated the compliance plan in the REMS supporting document. DRISK finds the proposed REMS modification for eculizumab and its appended materials (attached), and the supporting document, as submitted on June 24, 2019, to be acceptable.

1 Introduction

This review evaluates the proposed modification to the risk evaluation and mitigation strategy (REMS) for eculizumab (Soliris), BLA 125166/S-431, submitted by Alexion Pharmaceuticals (Alexion) on December 28, 2018. The Applicant submitted the REMS modification as part of a supplemental application for a new indication for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in (b) (4) who are anti-aquaporin-4 antibody-positive. The proposed modification consists of changes to the Prescriber Safety Brochure to add the NMOSD indication statement and to change the word order of the myasthenia gravis indication statement. The Applicant also updated the REMS compliance plan described in the REMS supporting document. The supplemental application is under review in the Division of Neurology Products (DNP).

2 Background

2.1 Product Information

Most patients with NMOSD have autoantibodies to the aquaporin-4 (AQP4) membrane protein expressed on astrocytes and in other areas of the central nervous system. Binding of the autoantibody to AQP4 results in activation of complement that initiates an inflammatory cascade resulting in axonal loss, demyelination, and the disease manifestations of NMOSD.[1,2] Eculizumab is a humanized monoclonal antibody that inhibits complement activation by binding to complement protein C5 and blocking its cleavage, thereby preventing the production of the terminal complement component C5a and the membrane attack complex C5b-9. The proposed eculizumab dose for the treatment of NMOSD is 900 mg

weekly by intravenous infusion for the first 4 weeks, followed by 1200 mg for the fifth dose one week later, followed by 1200 mg every 2 weeks thereafter.[a]

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.[b]

The REMS has been modified eight times for various reasons since approval. Two modifications were related to the approval of new indications for use, including the use of eculizumab for the treatment of atypical hemolytic uremic syndrome (aHUS) on September 23, 2011 and for the treatment of myasthenia gravis on October 23, 2017.

The goals of the currently approved REMS are:

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To educate Healthcare Professionals 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

The REMS consists of elements to assure safe use (ETASU), which include certification of prescribers to counsel and provide educational materials to patients, to immunize patients and provide antibiotic prophylaxis upon initiation of treatment if needed, and to report cases of meningococcal infection to the Applicant. Patients are required to receive counseling from the prescriber as well as vaccinations and antibiotic prophylaxis as directed. 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-431 relevant to this review:

- June 4, 2010: Eculizumab REMS approved.
- June 24, 2013: Orphan product designation granted for the treatment of neuromyelitis optica.
- December 28, 2018: Alexion submitted supplemental BLA 125166/S-431 for the use of eculizumab in the treatment of (b) (4) NMOSD who are anti-aquaporin-4 antibody-positive. The submission includes a proposed REMS modification that consists of a single change to the REMS appended materials to add the NMOSD indication statement to the Prescriber Safety Brochure. The submission

[a] The dose proposed for the treatment of NMOSD is the same as the dose currently approved for the treatment of atypical hemolytic uremic syndrome and the treatment of myasthenia gravis.
[b] Although never approved by the Agency, the Applicant voluntarily implemented their proposed RiskMAP after product launch.

did not include the assessment of an approved REMS required when submitting an efficacy supplement.[3]

- February 22, 2019: The Agency sent the Filing Communication Letter for S-431 to the Applicant. The letter included a request that Alexion submit a REMS assessment for a supplemental application for a new indication for use as described in the minutes of the pre-sBLA meeting held December 18, 2018.
- March 29, 2019: Alexion submitted the REMS assessment for a supplemental application for a new indication for use as a clinical information amendment to S-431.[4]
- May 14, 2019: The Agency sent an Information Request (IR) to Alexion about changes made to the REMS compliance plan described in the REMS supporting document submitted in S-431. The Agency requested additional information related to the operational and clinical aspects of emergency treatment with Soliris prescribed by non-certified prescribers, including the number of cases of meningococcal infection that have been reported in these situations.
- May 24, 2019: Alexion submitted a clinical information amendment to S-431 in response to the IR of May 14, 2019.[5]
- June 21, 2019: The Agency sent an IR to Alexion requesting submission of the following:
    - REMS document with the date of the most recent REMS update corrected to 06/2019
    - Prescriber Safety Brochure with the NMOSD indication statement aligned with the final version of the label. Additionally, change the word order of the myasthenia gravis indication statement to match the label.
    - REMS supporting document
    - A single, clean PDF of the REMS document compiled with all appended REMS materials
- June 24, 2019: Alexion submitted redlined and clean individual files of the REMS document and Prescriber Safety Brochure, the REMS supporting document, as well as the final REMS with the REMS document and all REMS materials compiled in a single file, to S-431.[6]

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Neuromyelitis optica spectrum disorder is a rare, inflammatory disorder of the CNS characterized by severe, immune-mediated demyelination and axonal damage that mainly targets the optic nerves and spinal cord. In most patients, the pathophysiology of NMOSD is related to an autoimmune process mediated by a disease-specific antibody referred to as the aquaporin-4 (AQP4) autoantibody. AQP4 is a water channel membrane protein expressed predominantly on astrocytes. Binding of the autoantibody to the receptor initiates AQP4 down-regulation, complement activation, inflammation, and astrocyte injury.[7,8]

The clinical features of NMOSD include acute attacks of optic neuritis leading to severe visual loss, and transverse myelitis that often causes symmetric paraparesis or quadriparesis, sensory loss, and bladder dysfunction. The disease typically follows a relapsing course. Attacks most often occur over days, with variable degrees of recovery over weeks to months. In some patients, optic neuritis and transverse myelitis occur concurrently, whereas in others, clinical findings are separated by a time delay. Central nervous system involvement outside of the optic nerves and spinal cord can also occur and may include

symptoms of intractable nausea, vomiting, hiccups, excessive daytime somnolence, reversible posterior leukoencephalopathy syndrome, neuroendocrine disorders, and (in children) seizures.[2]

The median age of disease onset is 32 to 41 years, but cases are also described in children as well as older adults. A study in Olmsted County, Minnesota estimated the prevalence rate to be 3.9 per 100,000 persons and a prevalence of approximately 17,000 persons in the U.S. at the end of 2011.[9]

3.2 Description of Current Treatment Options

There are no treatments currently approved for the NMOSD indication. Acute attacks and relapses are generally treated with intravenous glucocorticoids, such as high-dose methylprednisolone, followed by therapeutic plasma exchange for refractory or progressive symptoms. For long-term prevention of recurrent attacks, maintenance treatment with systemic immunosuppression is considered first-line therapy; the most commonly used treatments include azathioprine, mycophenolate mofetil, and rituximab. Azathioprine and mycophenolate typically require 4 to 6 months of use before onset of the biological effect and require bridging therapy with prednisone during this time. There are no controlled trials evaluating the treatment of NMOSD with these agents; the treatment recommendations are mainly supported by data from observational studies and by the clinical experience of experts. Observational evidence suggests multiple sclerosis disease-modifying therapies are ineffective or may aggravate NMOSD, and therefore must be avoided.

The treatments currently in use are associated with various adverse effects, some serious. Rituximab is associated with serious and potentially fatal infusion-related reactions, severe mucocutaneous reactions, hepatitis b virus reactivation, infections, and other serious reactions. Adverse effects of glucocorticoids include cataracts, hypertension, diabetes, and osteoporosis, among others. Azathioprine is associated with serious infections as well as hepatotoxicity, cytopenias, malignancies, and gastrointestinal toxicity. Serious adverse effects of mycophenolate include malignancies and infections; neutropenia can also occur.[10,11,12]

4 Benefit Assessment

The pivotal clinical study (ECU-NMO-301) supporting the application is a phase 3, randomized, double-blind, placebo-controlled study of eculizumab in 143 patients with a diagnosis of NMOSD who were positive for anti-AQP4 and who met additional criteria related to relapse history and disability scores.[c] Patients were randomized 2:1 to receive eculizumab (n=96) 900 mg intravenous once weekly for 4 weeks followed by a 1200 mg dose of eculizumab one week later and then every 2 weeks thereafter, versus placebo (n=47). All patients must have been vaccinated against N. meningitidis at least 14 days prior to receiving the first study drug dose or had been vaccinated and received treatment with appropriate antibiotics until 14 days after the vaccination. Patients completed the study once they experienced an on-trial relapse or once the end of study was reached, which was defined as 24 adjudicated relapses in 24 patients.

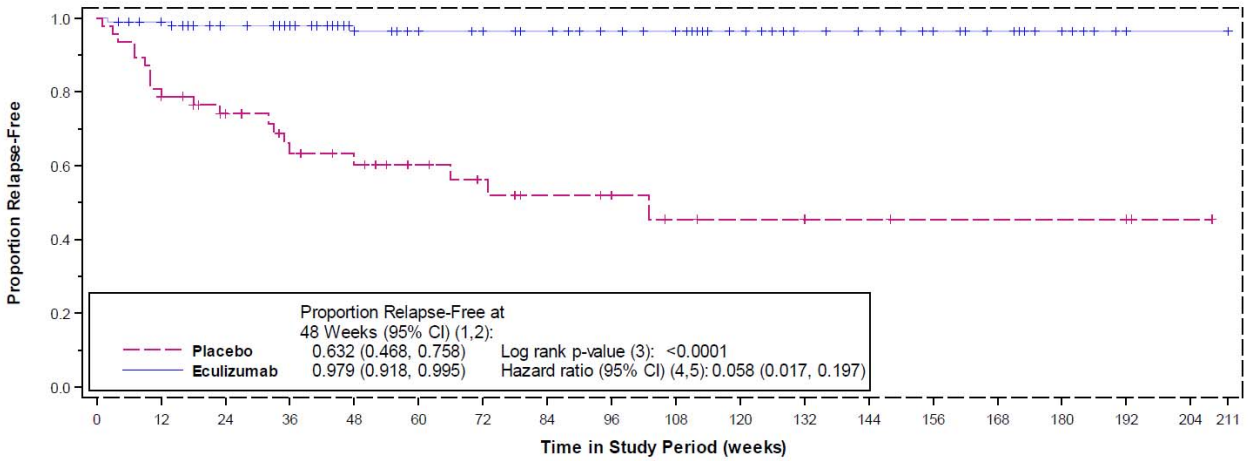
[c] Patients diagnosed with neuromyelitis optica (NMO) using earlier diagnostic criteria were also eligible to enroll.

Patients who completed ECU-NMO-301 were eligible to receive eculizumab in ECU-NMO-302, an open label extension study. At the time of the clinical database cutoff date, 39 patients had enrolled and been treated in the extension study. Twenty-five of the 39 patients were from the placebo/eculizumab group (who had received placebo in ECU-NMO-301) and 14 patients were from the eculizumab/eculizumab group (who had received eculizumab in ECU-NMO-301).

The primary efficacy endpoint in ECU-NMO-301 was the time to first adjudicated on-trial relapse. Secondary endpoints included the annualized relapse rate and disease-related disability as evaluated by the change from baseline at the end of study using several scales including the Expanded Disability Status Scale[d] (EDSS), Modified Rankin Scale[e] (mRS), and Hauser Ambulation Index[f] (HAI).

In the Phase 3 study, the first adjudicated on-trial relapse was observed in 3 of 96 patients (3.1%) in the eculizumab group and in 20 of 47 patients (42.6%) in the placebo group. A statistically significant effect on the time to first adjudicated relapse was observed for eculizumab compared with placebo ($p<0.0001$). The median time until the first adjudicated relapse was not reached in the eculizumab group and was reached at 103 weeks in the placebo group. The hazard ratio for eculizumab compared with placebo was 0.058 representing a 94.2% reduction in the risk of relapse ($p<0.0001$). The Kaplan-Meier estimates for the time to first adjudicated relapse in the two groups is shown in Figure 1 below.

Figure 1. Kaplan-Meier survival estimates for time to first adjudicated on-trial relapse



Source: Clinical Study Report ECU-NMO-301, Figure 14.2.1.1.1.

The adjudicated on-trial annualized relapse rate (ARR) in the eculizumab group was 0.16 compared with 0.35 in the placebo group. The adjusted ARR rate ratio for eculizumab to placebo was 0.045 ($p<0.0001$),

[d] The EDSS quantifies disability in 7 functional systems (pyramidal; cerebellar; brainstem; sensory; bowel and bladder; visual; and cerebral). The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death).

[e] The mRS is a scale used for measuring the degree of disability or dependence in the daily activities of people who have suffered from a neurological disability. The scale ranges from 0 (asymptomatic) to 6 (death).

[f] The HAI evaluates gait. This index is used to assess the time and effort used by the patient to walk 25 feet (8 meters). The scale ranges from 0 to 9, with 0 being the best score (asymptomatic; fully ambulatory with no assistance) and 9 being the worst score (restricted to wheel chair; unable to transfer self independently).

representing a 95.5% relative reduction in the rate of relapse for patients treated with eculizumab compared to placebo. Other secondary endpoints were nominally significant in favor of eculizumab except for the EDSS score, which showed a mean change from baseline to the end of study of -0.18 in the eculizumab group compared with 0.12 in the placebo group (p=0.0597).[13]

The clinical reviewer concluded that eculizumab demonstrates substantial evidence of efficacy in the treatment of NMOSD in adult patients who are positive for anti-AQP4.

5 Risk Assessment and Safe-Use Conditions

The NMOSD safety population is comprised of 143 patients who participated in the Phase 3 study and the open-label extension study, of which 121 patients were exposed to eculizumab.

5.1 Serious Adverse Events

There was one death in eculizumab-treated patients in the clinical development program. The case occurred in a 30-year-old male who developed congestive cardiac failure, pneumonia, infectious pleural effusion, respiratory failure, and sepsis after receiving two years of eculizumab. The patient had a history of chronic obstructive pulmonary disease, pulmonary fibrosis, morbid obesity, and other respiratory conditions, and was also receiving treatment with azathioprine.[14] The clinical reviewer considered the fatal outcome as being unlikely related to eculizumab therapy. No additional deaths were reported in the 90-day safety update.[15]

Overall there were 30 (31%) patients in the eculizumab group of Study ECU-NMO-301 who experienced 53 serious adverse events (SAEs) compared with 26 patients (55%) in the placebo group who experienced 47 SAEs. The most commonly reported SAE in each group was NMOSD (relapse), which was reported in 7 (7%) eculizumab-treated patients and 16 (34%) placebo-treated patients. Serious infections were reported in 6 patients in the placebo group, whereas 11 patients in the eculizumab group experienced 17 serious infections. The most frequently reported serious infections in eculizumab-treated patients were pneumonia (3), urinary tract infection (2), cellulitis (2), and sepsis (2).

In the open-label extension study, SAEs were experienced by 13 (33%) of 39 patients. The most common SAE was NMOSD (relapse), which was reported in 3 patients. Serious infections were reported in 7 patients (18%).

There were no reports of meningococcal infection in either ECU-NMO-301 or in the open-label extension. One patient experienced a Neisseria gonorrhea infection and sepsis, which occurred four days after receiving the first dose of eculizumab in the extension study. The patient was hospitalized, treated with antibiotics, and recovered.[14]

5.2 Severe Adverse Events

In Study ECU-NMO-301, 29 severe adverse events (AEs) were experienced by 17 (18%) patients in the eculizumab group compared with 22 severe adverse events that occurred in 12 (26%) patients in the placebo group. The most frequently reported severe AEs in the eculizumab group were back pain, pain in extremity, pneumonia, and NMOSD (relapse), which were experienced by 2 patients each. The most

frequently reported severe AE in the placebo group was NMOSD (relapse) in 6 (13%) patients. Severe infections were reported in 6 patients in the eculizumab group and one patient in the placebo group. The severe infections in eculizumab-treated patients included pneumonia (2), infectious pleural effusion, sepsis, cellulitis, appendicitis, Bartholin's abscess, gallbladder empyema, and hepatosplenic abscess. The severe infections reported in the placebo group patient included pneumococcal infection and pneumonia.

In the open-label extension study, severe AEs were experienced by 9 (23%) patients. The most frequently reported severe AEs were NMOSD (relapse) in 3 patients, and autoimmune thyroiditis and optic neuritis (2 patients each). Severe infections were reported in 3 patients and included urinary tract infection, Escherichia pyelonephritis, and Staphylococcal bacteremia.[14]

6 Expected Postmarket Use

Eculizumab is likely to be administered for the treatment of NMOSD in the outpatient setting in clinics, infusion centers, and physician offices. Home-based infusions are an additional option for patients who meet criteria set forth by payors, such as patients who have not previously experienced an infusion reaction to the drug. 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.[3] Additions of text are shown with underlining and deletions as strikethrough text.

7.1 REMS Document

Alexion proposes no changes other than an editorial change to the date of the most recent REMS update.

Reviewer comment: The date will need to be corrected to the date that the REMS modification is approved.

7.2 REMS Materials

7.2.1 Prescriber Enrollment Form

Alexion proposes no changes to the Prescriber Enrollment Form.

Reviewer comment: This is acceptable as there are no indication-specific sections in the enrollment form.

7.2.2 Prescriber Safety Brochure

Alexion proposes addition of the following under the Indication and Usage section:

The treatment of (b) (4) Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.

Reviewer comment: The proposed change is acceptable providing it aligns with the final version of the labeling. Additionally, DNP requested a change in the word order of the myasthenia gravis indication statement in the label, which should be reflected in the brochure.

7.2.3 PATIENT SAFETY CARD

Alexion proposes no changes to the Patient Safety Card.

Reviewer comment: This is acceptable as there are no indication-specific sections in the safety card.

7.2.4 PATIENT SAFETY BROCHURE

Alexion proposes no changes to the Patient Safety Brochure.

Reviewer comment: This is acceptable as there are no indication-specific sections in the patient safety brochure.

7.2.5 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

Alexion submitted changes to the compliance action plan that addresses the process of emergency orders received from non-certified prescribers, their subsequent enrollment efforts, and distribution of eculizumab. The new process, which was implemented October 12, 2018, involves the use of a third-party vendor who is responsible for prescriber enrollment and compliance. All prescribers will be required to certify except in life-threatening situations, for which the eculizumab order will be fulfilled regardless of the prescriber's certification status. Situations where a second (or more) exception is identified for a prescriber will be escalated and reviewed by Alexion drug safety senior leadership. After the Agency requested additional details about these processes, Alexion provided the following[5]:

- Since October 2018, there have been a total of 16 non-certified prescribers who have received an exception for emergency use. The patient must be hospitalized as an inpatient in a critical care situation to receive an emergency shipment of eculizumab ordered by a non-certified prescriber. All 16 prescribers subsequently became certified.
- No facility keeps a stock of eculizumab on hand for emergency situations. The drug is usually delivered within 8 hours of an order being placed.
- Two non-certified prescribers have received a second exception, each for the same patient during the same hospitalization. Each prescriber became certified within 2-5 days of the second exception.
- There have been no cases of meningococcal infection after exceptions for emergency use.

Reviewer comment: These processes are acceptable at this time. To maintain an awareness of the scope of the issue, it may be helpful to receive information about emergency use of eculizumab ordered by non-certified prescribers in future REMS assessment reports, which would require a revision to the current REMS assessment plan. This will be considered during review of the current REMS assessment report submitted to the BLA on May 28, 2019.

REMS Assessment Plan

Alexion proposes no changes to the current REMS assessment plan, which was approved July 25, 2018. The timetable for submission of assessments is to remain every two years as stated in the currently approved REMS.

Reviewer comment: This is acceptable.

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) NMOSD. The proposed modification consists of changes to the Prescriber Safety Brochure to add the NMOSD indication statement and to change the word order of the myasthenia gravis indication statement. Otherwise, the REMS document and materials do not require revision because the REMS-related risks of treatment for the new indication are not different from the approved indications.

The clinical reviewer concluded that substantial evidence of clinical efficacy has been established for the use of eculizumab for the treatment of NMOSD in adult patients who are positive for anti-AQP4.

Neuromyelitis optica spectrum disorder is a rare, relapsing, inflammatory disorder of the CNS characterized by severe, immune-mediated demyelination and axonal damage that mainly targets the optic nerves and spinal cord. In most patients, the pathophysiology of NMOSD is related to an autoimmune process mediated by an aquaporin-4 (AQP4) autoantibody and activation of the complement system. The pivotal clinical study found a significant effect on the time to first adjudicated on-trial relapse for eculizumab compared with placebo. The hazard ratio for eculizumab compared with placebo was 0.058 representing a 94.2% reduction in the risk of relapse. The adjusted ARR rate ratio also showed a significant relative reduction in the rate of relapse for patients treated with eculizumab compared to placebo.

Based on the drug's mechanism of action, the most serious risk of eculizumab in treating NMOSD is that of meningococcal infection, which requires a REMS with ETASU for the currently approved indications. Additional risks include other serious infections, particularly with encapsulated organisms, and the potential for hypersensitivity or infusion reactions, which is an inherent risk with monoclonal antibody infusions.

Per section 505-1(g)(2)(A) of the FDCA, an Applicant is required to submit an assessment of an approved REMS when submitting a supplemental application for a new indication for use. Alexion's submission of this assessment concluded that no new risks are introduced with the NMOSD indication, and thus, the benefit-risk profile of eculizumab remains the same as for the approved indications (using the general concept of benefit, not disease-specific benefit). The clinical reviewer agreed that the benefit-risk profile

does not change with the new indication.[g] DRISK expects the REMS modification will not create unnecessary burden on prescribers or adversely affect access to eculizumab for patients with NMOSD.

The Applicant did not propose any revisions to the REMS assessment plan but included changes (which were implemented in October 2018) to the compliance action plan in the REMS supporting document. These changes mainly address the process of emergency orders received from non-certified prescribers, their subsequent enrollment efforts, and distribution of eculizumab. We find these processes to be acceptable at this time, but the addition of metrics related to emergency use of eculizumab by non-certified prescribers may be useful information in future REMS assessment reports and will be considered as additions to the Assessment Plan during the review of the REMS assessment submitted in May 2019.

9 Recommendations

DRISK finds the proposed REMS modification for Soliris (attached) as submitted on June 24, 2019, acceptable.

DRISK recommends approval of the REMS appended to this review.

[g] Personal email communication, Larry Rodichok, DNP, May 29, 2019.

10 Appendix

10.1 REFERENCES

[1] Alexion. Clinical overview for eculizumab, BLA 125166 S-431, December 28, 2018.

[2] Glisson CC. Neuromyelitis optica spectrum disorders. In:UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA 2019.

[3] Alexion. REMS Modification for eculizumab, BLA 125166 S-431, December 28, 2018.

[4] Alexion. Clinical Response to Information Request, BLA 125166 S-431, March 29, 2019.

[5] Alexion. Clinical Response to Information Request, BLA 125166 S-431, May 24, 2019.

[6] Alexion. Clinical Response to Information Request, Final REMS, BLA 125166 S-431, June 24, 2019.

[7] Weinshenker BG and Wingerchuk DM. Neuromyelitis Spectrum Disorders. Mayo Clin Proc 2017; 92:663-679.

[8] Hinson SR, et al. Molecular outcomes of neuromyelitis optica (NMO)-IgG binding to aquaporin-4 in astrocytes. PNAS 2012; 109:1245-1250.

[9] Flanagan EP, et al. Epidemiology of Aquaporin-4 Autoimmunity and Neuromyelitis Optica Spectrum. Ann Neurol 2016; 79:775–783.

[10] Azathioprine, Prescribing Information, accessed online at https://dailymed.nlm.nih.gov/dailymed/ March 25, 2019.

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/s/

ROBERT G PRATT
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DONELLA A FITZGERALD
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LAURA A ZENDEL on behalf of JAMIE C WILKINS PARKER
06/26/2019 03:19:48 PM