

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125166s172

Trade Name: Soliris

Generic Name: Eculizumab

Sponsor: Alexion Pharmaceuticals, Inc.

Approval Date: September 23, 2011

Indication: For the treatment of atypical hemolytic uremic syndrome (aHUS)

CENTER FOR DRUG EVALUATION AND RESEARCH

125166s172

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125166s172

APPROVAL LETTER



Our STN: BL 125166/172

**SUPPLEMENTAL BLA ACCELERATED APPROVAL
REMS ASSESSMENT INCOMPLETE
REMS MODIFICATION APPROVAL**

September 23, 2011

Alexion Pharmaceuticals, Inc.
Attention: Claude Nicaise, M.D.
Senior Vice President of Strategic Development
And Regulatory Affairs
352 Knotter Drive
Cheshire, CT 06410

Dear Dr. Nicaise:

Please refer to your Supplemental Biologics License Application (sBLA), dated March 25, 2011, received March 25, 2011, submitted under section 351 of the Public Health Service Act for Soliris[®] (eculizumab).

We acknowledge receipt of your amendments dated April 5, 2011, April 25, 2011, April 29, 2011, May 17, 2011, May 24, 2011, May 27, 2011, June 3, 2011, June 8, 2011, June 9, 2011, June 10, 2011, July 19, 2011, July 20, 2011, and July 26, 2011, and your risk evaluation and mitigation strategy (REMS) assessment dated May 31, 2011.

This "Prior Approval" efficacy supplement to your biologics license application provides for the treatment of atypical Hemolytic Uremic Syndrome (aHUS), as a second indication for Soliris[®] (eculizumab).

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

We also refer to your May 31, 2011, submission containing your assessment of the Soliris[®] (eculizumab) risk evaluation and mitigation strategy (REMS). After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be incomplete in that you did not submit patient and prescriber surveys. In addition, the assessment showed a low rate of prescriber enrollment into the REMS. Therefore, modifications have been made to the REMS to increase prescriber enrollment.

CONTENT OF LABELING

Within 14 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm> that is identical in content to the enclosed labeling text. The content of labeling should be submitted by updating your application by referencing the SPL file submitted to the drug establishment registration and drug listing system. To do this, place a link in your application submission that directs FDA to your SPL file. For administrative purposes, please designate this submission “**Product Correspondence – Final SPL for approved STN BLA 125166/172.**”

In addition, within 14 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement. For additional information on submitting labeling to drug establishment registration and drug listing and to applications, see the FDA guidances at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072339.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

ACCELERATED APPROVAL REQUIREMENTS

As requested in your letter of March 25, 2011, marketing approval of this product is granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as bases for approvals of products intended for serious or life-threatening illnesses or conditions.

Approval under these regulations requires, among other things, that you conduct adequate and well-controlled trials to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as increased survival or improvement in disease-related symptoms. You are required to conduct such trials with due diligence. If postmarketing trials fail to verify that clinical benefit is conferred by Soliris, or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw or modify approval. Granting of this approval is contingent upon completion of clinical trials to verify the

clinical benefit of Soliris, as outlined in your letter of September 1, 2011. These trials are subject to the reporting requirements of 21 CFR 601.70:

1. **PMR 172/1:** An open-label, multi-center clinical trial of eculizumab in pediatric patients with atypical hemolytic uremic syndrome. This trial will be amended to include pharmacokinetic, efficacy and safety data from a minimum of five patients who are treated with eculizumab in each of the following age cohorts:

- 1 month to < 24 months
- 2 to < 5 years
- 5 to 12 years.

Final Protocol Submission Date: November 2011
Trial Completion Date: December 2013
Final Report Submission Date: September 2014

2. **PMR 172/2:** An open-label, multi-center clinical trial of eculizumab in adult patients with atypical hemolytic uremic syndrome. This trial will enroll a minimum of 30 patients.

Final Protocol Submission Date: June 2011
Trial Completion Date: December 2012
Final Report Submission Date: September 2013

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of September 1, 2011.

For administrative purposes, all submissions related to these postmarketing trials should be clearly designated "Subpart E Postmarketing Study Commitments".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Soliris® (eculizumab) was approved on March 16, 2007, we have become aware of the serious risk of meningococcal and other infections with Soliris® (eculizumab), based upon postmarketing information. Additionally, in patients with atypical hemolytic uremic syndrome, there is a need to further assess the potential risk of secondary malignancies and of potential complications related to the use of Soliris® (eculizumab) in pregnancy. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known risk of serious infections, the serious risks of secondary malignancies, and the potential complications

associated with use of Soliris® (eculizumab) in pregnancy. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 172/3: Evaluate the long-term safety of eculizumab by enrolling all patients with aHUS treated with eculizumab in a Soliris registry program and analyzing outcomes for a period of no less than five years. Submit interim reports annually to the BLA including the specific items listed below. At the end of the five-year period, submit a final report to the BLA that describes the major safety findings from this registry, including the specific items listed below, and propose labeling changes as appropriate. The following data will be collected for each patient receiving eculizumab for the treatment of aHUS:

- Serious infections, defined as infections necessitating or prolonging hospitalization, or resulting in death. Alexion will collect follow-up information from these patients to assess the nature of the serious infection, the major features of the clinical course, and the survival status.
- Malignancy, including the nature of the malignancy and the survival status of patients who develop a malignancy.
- Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among babies born to women exposed to eculizumab during the pregnancy.
- Survival
- Occurrence of stroke (yes/no)
- Requirement for renal transplant (yes/no)
- New dialysis requirement or increase in the frequency of dialysis (yes/no)
- aHUS exacerbation requiring plasma therapy (yes/no)
- Discontinuation (yes/no) and, if discontinued, the reason for discontinuation.

The timetable you submitted on September 1, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	November 2011
Interim report:	November 2012
Interim report:	November 2013
Interim report:	November 2014
Interim report:	November 2015
Study Completion:	December 2016
Final Report Submission:	September 2017

Submit the protocol to your IND 11075, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Soliris[®] (eculizumab) was originally approved on June 4, 2010. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of revisions to the REMS document, Medication Guide, and appended REMS materials. These modifications are to provide consistency with the revised package insert and to revise the REMS document and the REMS materials to facilitate prescriber certification in the REMS.

Your proposed modified REMS, submitted on September 19, 2011, as amended, and appended to this letter is approved.

The timetable for submission of assessments of the REMS will remain the same as approved on June 4, 2010.

The revised REMS assessment plan should include, but is not limited to, the following:

1. Assessment of enrollment and discontinuation statistics for patients and prescribers
 - The number of patients enrolled in the OneSource Safety Support Program and receiving Soliris treatment (during the reporting period and cumulative)
 - The number of patient person-years for enrolled patients on Soliris
 - The number of new patients enrolled during the reporting period
 - The number of patients who received Soliris who were not enrolled (during the reporting period and cumulative)

- The number of patients who discontinued Soliris (during the reporting period and cumulative)
 - The number of patients who were lost to follow up (during the reporting period and cumulative)
 - Prescriber enrollment:
 - Numbers enrolled: total and newly enrolled during the reporting period,
 - Number who are prescribing Soliris who are not enrolled
 - Reasons that prescribers did not enroll
 - Actions taken to ensure that all prescribers are enrolled
2. An assessment of the following use data for Soliris
- The number of patients treated by diagnosis
 - Number of pediatric patients
 - The percent of patients receiving meningococcal vaccination
3. The number and summary of prescribers who were un-enrolled from the OneSource Safety Support Program during the reporting period and cumulatively.
4. A narrative summary and analysis of meningococcal infections during the reporting period; this will include for each case:
- The serotype of *Neisseria meningitides*
 - The type and timing of vaccination and revaccination against *Neisseria meningitides*
 - The circumstances under which the patient sought/received treatment for meningococcal infection, including the patient's use of the Soliris Patient Safety Card
 - The clinical course of the meningococcal infection, and the outcome of the infection
5. An assessment of prescriber and patient understanding regarding the safe use of Soliris i.e., the results of surveys administered to prescribers and patients.
6. Medication Guide distribution data, including the number of Medication Guides dispensed in comparison to the number of prescriptions shipped during the reporting period, a report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR208.24, a report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
7. Based on the information submitted, an assessment of and conclusion regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

8. Additionally, submit by March 1, 2012, a report on your progress on increasing prescriber enrollment. This report should include the following data as of 120 days following approval of the REMS modification:
 - Numbers of prescribers enrolled: total enrolled and newly enrolled during the 120 days following approval of the REMS modification.
 - Number who are prescribing Soliris who are not enrolled
 - Reasons that prescribers did not enroll
 - Actions taken to ensure that all prescribers are enrolled
9. An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
10. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 21 CFR 601.70 and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

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

BLA 125166 REMS ASSESSMENT

**NEW SUPPLEMENT FOR BLA 125166
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125166
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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 package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

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).

We request expedited reporting (15 day telephone or facsimile Medwatch communication) for the occurrence of serious infections, including those identified in the Soliris[®] (eculizumab) registry program.

If you have any questions, contact the Senior Regulatory Project Manager, Ebla Ali Ibrahim, at (301) 796-3691.

Sincerely,

A handwritten signature in black ink, appearing to read "Ann T. Farrell, M.D.", written in a cursive style.

/Ann T. Farrell, M.D./

Ann T. Farrell, M.D.

Acting Division Director

Division of Hematology Products

Office of Hematology Oncology Products

Center for Drug Evaluation and Research

Enclosure
Content of Labeling
REMS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125166s172

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)

Concentrated solution for intravenous infusion

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. Meningococcal infection 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.
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* (5.1) for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program (5.2). Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747).

RECENT MAJOR CHANGES

Box Warning	9/2011
Indications and Usage (1.2)	9/2011
Contraindications (4)	9/2011
Dosage and Administration (2.2)	9/2011
Warnings and Precautions (5.3, 5.4 and 5.6)	9/2011
Adverse Reactions (6.1)	9/2011
Use in Specific Populations (8.4)	9/2011
Clinical Studies (14.2)	9/2011
Patient Counseling Information (17)	9/2011

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).
- The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function.

Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

DOSAGE AND ADMINISTRATION

Only administer as an intravenous infusion

PNH Dosage Regimen: (2.1)

aHUS Dosage Regimen: (2.2)

DOSAGE FORMS AND STRENGTHS

300 mg single-use vials each containing 30 mL of 10 mg/mL sterile, preservative-free solution (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.
- 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 (≥15% combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia (6.1).

USE IN SPECIFIC POPULATIONS

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

Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3).

Pediatric Use: PNH: safety and effectiveness not established. aHUS: safety and effectiveness similar to adult patients (8.4).

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-888-SOLIRIS (1-888-765-4747) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide.

Revised: 09/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 (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 a meningococcal vaccine 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 *Serious Meningococcal Infections (5.1)* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program (5.2). Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747).

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.

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

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

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

Only administer as an intravenous infusion.

2.1 Recommended Dosage Regimen - PNH

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.

Soliris should be administered at the recommended dosage regimen time points, or within two days of these time points [see *Warnings and Precautions (5.6)*].

2.2 Recommended Dosage Regimen - aHUS

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

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

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

Table 1: Dosing recommendations in patients less than 18 years of age

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

5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

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

Supplemental dosing of Soliris is required in the setting of concomitant support with PE/PI (plasmapheresis or plasma exchange; or fresh frozen plasma infusion) (Table 2).

Table 2: Supplemental dose of Soliris after PE/PI

Type of Intervention	Most Recent Soliris Dose	Supplemental Soliris Dose With Each PE/PI Intervention	Timing of Supplemental Soliris Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	600 mg or more	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	300 mg or more	300 mg per each unit of fresh frozen plasma	60 minutes prior to each 1 unit of fresh frozen plasma infusion

2.3 Preparation and Administration

Soliris must be diluted 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. The Soliris admixture should be inspected visually for particulate matter and discoloration prior to administration.

2.4 Administration

Do Not Administer As An Intravenous Push or Bolus Injection

The Soliris admixture should be administered by intravenous infusion over 35 minutes via gravity feed, a syringe-type pump, or an infusion pump. Admixed solutions of Soliris are stable for 24 hours 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. 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

Soliris is supplied as 300 mg single-use vials each containing 30 mL of 10 mg/mL sterile, preservative-free eculizumab solution.

4 CONTRAINDICATIONS

Soliris is contraindicated in:

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

5 WARNINGS AND PRECAUTIONS

5.1 Serious Meningococcal Infections

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

Administer a polyvalent meningococcal vaccine 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.

Vaccinate 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 the meningococcal vaccine as soon as possible. In clinical studies, 33/67 patients with aHUS were treated with Soliris less than 2 weeks after meningococcal vaccination and 31 of these 33 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, a previously vaccinated patient with aHUS developed meningococcal sepsis during the post-study follow-up period [*see Adverse Reactions (6.1)*].

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

5.2 Soliris REMS

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

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

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

5.3 Other Infections

Soliris blocks terminal complement activation; therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. 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.

5.4 Monitoring 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 studies, 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 reinstatement of Soliris treatment, plasma therapy [plasmapheresis, plasma exchange, or fresh frozen plasma infusion (PE/PI)], or appropriate organ-specific supportive measures.

5.5 Thrombosis Prevention and Management

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

5.6 Laboratory Monitoring

PNH

Serum LDH levels increase during hemolysis and may assist in monitoring Soliris effects, including the response to discontinuation of therapy. In clinical studies, six patients achieved a reduction in serum LDH levels only after a decrease in the Soliris dosing interval from 14 to 12 days. All other patients achieved a reduction in serum LDH levels with the 14 day dosing interval [see *Clinical Pharmacology (12.2) and Clinical Studies (14.1)*].

aHUS

Early signs of thrombotic microangiopathy (TMA) include a decrease in platelet count, and increases in serum LDH and creatinine levels. Follow patients for signs of TMA by monitoring serial platelet counts, serum LDH, and creatinine during Soliris therapy and following discontinuation of Soliris.

5.7 Infusion Reactions

As with all protein products, 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

6.1 Clinical Trial Experience

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 (in which 43 patients received Soliris and 44, placebo); a single arm clinical study and a long term extension study. 182 patients were exposed for greater than one year. All patients received the recommended Soliris dose regimen.

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. 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 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 two prospective, single-arm studies (aHUS Studies 1 and 2) and one retrospective study (aHUS Study 3). The data described below were derived from 37 adult and adolescent patients with aHUS enrolled in aHUS Study 1 and aHUS Study 2. All patients received the recommended dosage of Soliris. Median exposure was 38 weeks (range: 2-64 weeks).

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. Table 5 summarizes all adverse events reported in at least 10% of patients in aHUS Studies 1 and 2 combined.

Table 5: Per Patient Incidence of Adverse Events in Adult and Adolescent Patients Enrolled in aHUS Study 1 and aHUS Study 2 Separately and in Total

MedDRA ver. 11.0	Number (%) of Patients		
	Study 1 (n=17)	Study 2 (n=20)	Total (n=37)

MedDRA ver. 11.0	Number (%) of Patients		
	Study 1 (n=17)	Study 2 (n=20)	Total (n=37)
Vascular Disorders			
Hypertension ^a	8(47)	5 (25)	13 (35)
Infections and Infestations			
Upper respiratory tract infection ^b	5 (29)	8 (40)	13(35)
Urinary tract infection	4 (24)	2 (10)	6 (16)
Gastrointestinal Disorders			
Diarrhea	6 (35)	6 (30)	12 (32)
Vomiting	5 (29)	3 (15)	8 (22)
Nausea	4 (24)	3 (15)	7 (19)
Abdominal pain	0	4 (20)	4 (11)
Nervous System Disorders			
Headache	7 (41)	4 (20)	11 (30)
Blood and Lymphatic System Disorders			
Anemia	6 (35)	3 (15)	9 (24)
Leukopenia	4 (24)	2 (10)	6 (16)
Psychiatric Disorders			
Insomnia	4 (24)	1 (5)	5 (14)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	2 (12)	3 (15)	5 (14)
Pharyngolaryngeal pain	1 (6)	4 (20)	5 (14)
General Disorders and Administration Site Conditions			
Fatigue	3 (18)	1 (5)	4 (11)
Peripheral edema	3 (18)	1 (5)	4 (11)
Pyrexia	3 (18)	1 (5)	4 (11)
Ear and Labyrinth Disorders			
Vertigo	1 (6)	3 (15)	4 (11)
Musculoskeletal and Connective Tissue Disorders			
Pain in extremity	1 (6)	3 (15)	4 (11)

^a includes the preferred terms hypertension, accelerated hypertension, and malignant hypertension.

^b includes the preferred terms upper respiratory tract infection and nasopharyngitis.

In aHUS Studies 1 and 2 combined, 54% (20/37) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were hypertension (16%) and infections (14%). One patient discontinued Soliris due to adverse events deemed unrelated to Soliris.

Analysis of retrospectively collected adverse event data from pediatric and adult patients enrolled in aHUS Study 3 (N=30) revealed a safety profile that was similar to that which was observed in the two prospective studies. aHUS Study 3 included 19 pediatric patients less than 18 years of age. Overall, the safety of Soliris in pediatric patients with aHUS

enrolled in Study 3 appeared similar to that observed in adult patients. The most common ($\geq 15\%$) adverse events occurring in pediatric patients are presented in Table 6.

Table 6: Adverse Reactions Occurring in at Least 15% of Patients Less than 18 Years of Age Enrolled in aHUS Study 3

MedDRA ver. 11.0	Number (%) of Patients			Total (n=19)
	< 2 yrs (n=5)	2 to < 12 yrs (n=10)	12 to <18 yrs (n=4)	
General Disorders and Administration Site Conditions				
Pyrexia	4 (80)	4 (60)	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				
Tachycardia	2 (40)	2 (20)	0 (0)	4 (21)

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

6.2 Immunogenicity

As with all proteins there is a potential for immunogenicity. 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 electrochemiluminescence (ECL) bridging assay using the eculizumab whole molecular as target was used for the aHUS indication. Low titers of antibodies to Soliris were detected in 3/196 (2%) of all PNH patients treated with Soliris by the ELISA assay. In patients with aHUS treated with Soliris, antibodies to Soliris were detected in 1/37 (2.7%) by the ECL assay. An ECL based neutralizing HAHA assay with a low sensitivity of 2 mcg/mL was performed to detect neutralizing antibodies for the 37 patients with aHUS. No neutralizing activity to Soliris was detected in patients with aHUS treated with Soliris. No apparent correlation of antibody development to clinical response was observed in both indications. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Soliris in an ELISA based assay and/or an ECL based assay are highly dependent on the sensitivity and specificity of the assay used. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the

incidence of antibodies to Soliris with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

Cases of serious or fatal meningococcal infections have been reported.

7 DRUG INTERACTIONS

Drug interaction studies have not been performed with Soliris.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies of Soliris in pregnant women. Soliris, a recombinant IgG molecule (humanized anti-C5 antibody), is expected to cross the placenta. Animal studies using a mouse analogue of the Soliris molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and moribund offspring at doses 2-8 times the human dose. Soliris should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

8.3 Nursing Mothers

It is not known whether Soliris is excreted into human milk. IgG is excreted in human milk, so it is expected that Soliris will be present in human milk. However, published data suggest that antibodies in human milk do not enter the neonatal and infant circulation in substantial amounts. Caution should be exercised when Soliris is administered to a nursing woman. The unknown risks to the infant from gastrointestinal or limited systemic exposure to Soliris should be weighed against the known benefits of human milk feeding.

8.4 Pediatric Use

The safety and effectiveness of Soliris for the treatment of PNH in pediatric patients below the age of 18 years have not been established.

Three clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS included a total of 25 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 *Dosage and Administration* (2.2), *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

Sixteen patients 65 years of age or older (15 with PNH and 1 with aHUS) were treated with Soliris. 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.

10 OVERDOSAGE

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

11 DESCRIPTION

Soliris, a complement inhibitor, is a formulation of eculizumab which is a recombinant humanized monoclonal IgG2/4_κ antibody produced by murine myeloma cell culture and purified by standard bioprocess technology. Eculizumab contains human constant regions from human IgG2 sequences and human IgG4 sequences and murine complementarity-determining regions grafted onto the human framework light- and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eculizumab, the active ingredient in Soliris, is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Soliris inhibits terminal complement mediated intravascular hemolysis in PNH patients and complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS.

A genetic mutation in patients with PNH leads to the generation of populations of abnormal RBCs (known as PNH cells) that are deficient in terminal complement inhibitors, rendering PNH RBCs sensitive to persistent terminal complement-mediated destruction. The destruction and loss of these PNH cells (intravascular hemolysis) results in low RBC counts (anemia), and also fatigue, difficulty in functioning, pain, dark urine, shortness of breath, and blood clots.

In aHUS, impairment in the regulation of complement activity leads to uncontrolled terminal complement activation, resulting in platelet activation, endothelial cell damage and thrombotic microangiopathy.

12.2 Pharmacodynamics

In the PNH placebo-controlled clinical study, Soliris when administered as recommended reduced hemolysis as shown by the reduction of serum LDH levels from 2200 ± 1034 U/L (mean $\pm$ 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 the single arm clinical study, Soliris maintained this effect through 52 weeks [see *Clinical Studies (14)*].

12.3. Pharmacokinetics

A population PK analysis with a standard 1-compartmental model was conducted on the multiple dose PK data from 40 PNH patients receiving the recommended Soliris regimen [see *Dosage and Administration (2.1)*]. In this model, the clearance of Soliris for a typical PNH patient weighing 70 kg was 22 mL/hr and the volume of distribution was 7.7 L. The half-life was 272 ± 82 hrs (mean $\pm$ SD). The mean observed peak and trough serum concentrations of Soliris by week 26 were 194 ± 76 mcg/mL and 97 ± 60 mcg/mL, respectively.

A second population PK analysis with a standard 1 compartmental model was conducted on the multiple dose PK data from 57 aHUS patients receiving the recommended Soliris regimen in studies 1, 2 and 3. In this model, the clearance of Soliris for a typical aHUS patient weighing 70 kg was 14.6 mL/hr and the volume of distribution was 6.14 L. The elimination half-life was 291 h (approximately 12.1 days).

The clearance and half-life of eculizumab were also evaluated during plasma exchange interventions. Plasma exchange increased the clearance of eculizumab to 3660 mL/hr and reduced the half-life to 1.26 hours. Supplemental dosing is recommended when Soliris is administered to aHUS patients receiving plasma infusion or exchange [see *Recommended Dosage Regimen (2.1)*].

Dedicated studies have not been conducted to evaluate the PK of Soliris in special patient populations identified by gender, race, age (pediatric or geriatric), or the presence of renal or hepatic impairment. Pediatric and adolescent patients (less than 18 years of age) and patients with renal impairment were included in the aHUS clinical studies [see *Clinical Studies (14)*]. Population PK analysis showed age, gender, race, and renal function do not influence the PK of eculizumab.

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 PNH

The safety and efficacy of Soliris in PNH patients with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26 week study (Study 1); PNH patients were also treated with Soliris in a single arm 52 week study (Study 2); and in a long term extension study. 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.

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 7).

Table 7: PNH Study 1 Patient Baseline Characteristics

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

Patients treated with Soliris had significantly reduced ($p < 0.001$) hemolysis resulting in improvements in anemia as indicated by increased hemoglobin stabilization and reduced need for RBC transfusions compared to placebo treated patients (see Table 8). 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 8: 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

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 aHUS

Three single-arm studies [(two prospective (aHUS Studies 1 and 2) and one retrospective (aHUS Study 3)] 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 aHUS Study 3 was based on body weight [see *Recommended Dosage Regimen* (2.2)]. Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints.

Endpoints related to TMA included the following:

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

aHUS Resistant to PE/PI (aHUS Study 1)

aHUS Study 1 enrolled patients who displayed signs of thrombotic microangiopathy (TMA) despite receiving at least four PE/PI treatments the week prior to screening. One patient had no PE/PI the week prior to screening because of PE/PI intolerance. In order to qualify for enrollment, patients were required to have a platelet count $\leq 150 \times 10^9/L$, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above

the upper limits of normal, without the need for chronic dialysis. The median patient age was 28 (range: 17 to 68 years). Patients enrolled in aHUS Study 1 had an ADAMTS-13 level above 5%. Seventy-six percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 9 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS Study 1.

Table 9: Baseline Characteristics of Patients Enrolled in aHUS Study 1

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

Patients in aHUS Study 1 received Soliris for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients continued to receive Soliris by enrolling into an extension study. In aHUS Study 1, the median duration of Soliris therapy was approximately 38 weeks (range: 2 weeks to 64 weeks).

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 aHUS Study 1, mean platelet count increased from $109 \pm 32 \times 10^9/L$ at baseline to $169 \pm 72 \times 10^9/L$ by one week; this effect was maintained through 26 weeks (mean platelet count at week 26: $210 \pm 68 \times 10^9/L$). Table 10 summarizes the efficacy results for aHUS Study 1.

Table 10: Efficacy Results for aHUS Study 1 in PE/PI-Resistant aHUS

Efficacy Parameter	aHUS Study 1 N=17
Change in platelet count from baseline through week 26 ($\times 10^9/L$), least square mean (95% CI) ¹	73 (40-105)
Hematologic normalization ² , n (%)	13 (76)
Median Duration of hematologic normalization, weeks (range) ²	37 (25, 62)
Complete TMA response, n (%)	11 (65)
Median Duration of complete TMA response, weeks (range) ²	38 (25, 56)
TMA event-free status, n (%)	15 (88)

Efficacy Parameter	aHUS Study 1 N=17
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	0.88 (0.04, 1.59) 0 (0, 0.31)
Change in eGFR (mL/min/1.73 m ²) at 26 weeks, median (range)	+20 (-1, 98)
eGFR improvement ≥ 15 mL/min/1.73 m ² , n (%) ¹ Median duration of eGFR improvement, days (range) ²	9 (53) 251 (70-392)

¹ Calculated at each post-dose day of measurement (excluding Days 1 to 4) through Week 26 using a repeated measurement ANOVA model.

² At data cut-off (September 8, 2010).

Renal function, as measured by median eGFR, was improved during Soliris therapy. Four of the five patients who required dialysis at study entry were able to discontinue dialysis for the duration of Soliris treatment, and one patient developed a new dialysis requirement.

In aHUS Study 1, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

aHUS Sensitive to PE/PI (aHUS Study 2)

aHUS Study 2 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 aHUS Study 2. The median patient age was 28 years (range: 13 to 63 years). Patients enrolled in aHUS Study 2 had an ADAMTS-13 level above 5%. Seventy percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 11 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS Study 2.

Table 11: Baseline Characteristics of Patients Enrolled in aHUS Study 2

Parameter	aHUS Study 2 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 aHUS Study 2 received Soliris for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients continued to receive Soliris by enrolling into an extension study. In aHUS Study 2, the median duration of Soliris therapy was approximately 40 weeks (range: 26 to 52 weeks). Table 12 summarizes the efficacy results for aHUS Study 2.

Table 12: Efficacy Results for aHUS Study 2 in PE/PI-Sensitive aHUS

Efficacy Parameter	aHUS Study 2 N=20
TMA Event-free status n (%) (95% CI) ¹	16 (80) (56 - 94)
Daily TMA intervention rate, median (range)	
Before eculizumab	0.23 (0.05, 1.09)
On eculizumab treatment	0
Change in platelet count from baseline through week 26 ($\times 10^9/L$), least square mean (95% CI) ¹	5 (-17.5 - 28)
Hematologic normalization ² , n (%)	18 (90)
Median duration of hematologic normalization, weeks (range) ³	38 (22, 52)
Complete TMA response, n (%)	5 (25)
Median duration of complete TMA response, weeks (range) ³	32 (12, 38)
Change in eGFR (mL/min/1.73 m ²) at 26 weeks, median (range)	+5 (-1, 20)
eGFR improvement ≥ 15 mL/min/1.73 m ² , n (%)	1 (5)

¹ Calculated at each post-dose day of measurement (excluding Days 1 to 4) through Week 26 using a repeated measurement ANOVA model.

² In aHUS Study 2, 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.

³ At data cut-off (October 10, 2010).

In aHUS Study 2, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins. 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. Platelet counts were maintained at normal levels despite the elimination of PE/PI. The mean platelet count was $229 \pm 78 \times 10^9/L$ at baseline, and $233 \pm 69 \times 10^9/L$ at week 26. Renal function, as measured by median eGFR, was maintained during Soliris therapy. No patient required new dialysis with Soliris.

Retrospective Study in Patients with aHUS (aHUS Study 3)

The efficacy results for the aHUS retrospective study (aHUS Study 3) 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 increased from $171 \pm 83 \times 10^9/L$ at baseline to 233

$\pm 109 \times 10^9/L$ after one week of therapy; this effect was maintained through 26 weeks (mean platelet count at week 26: $254 \pm 79 \times 10^9/L$).

A total of 19 pediatric patients (ages 2 months to 17 years) received Soliris in aHUS Study 3. 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 17 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 aHUS Studies 1 and 2 (Table 13). No pediatric patient required new dialysis during treatment with Soliris.

Table 13: Efficacy Results in Pediatric Patients Enrolled in aHUS Study 3

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

¹ Platelet count normalization was defined as a platelet count of at least $150,000 \times 10^9/L$ 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 m², one received dialysis throughout the study period and another received eculizumab as prophylaxis following renal allograft transplantation.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

Soliris vials must be stored in the original carton until time of use under refrigerated conditions at 2-8° C (36-46° F) and protected from light. Do not use beyond the expiration date stamped on the carton. Refer to *Dosage and Administration* (2) for information on the stability and storage of diluted solutions of Soliris.

DO NOT FREEZE. DO NOT SHAKE.

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

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.

Patients should be informed that they are required to receive a 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 vaccine use while on Soliris therapy. Patients should also be informed that vaccination may not prevent meningococcal infection. Patients should be educated about any of the signs and symptoms of meningococcal infection, and strongly advised 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 of 103° F (39.4° C) or higher
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Patients should be informed 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.

Patients should also be informed that there may be an increased risk of other types of infections, particularly those due to encapsulated bacteria. Parents or caregivers of children receiving Soliris for the treatment of aHUS should be informed that their child should be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) according to current medical guidelines.

Patients with PNH should be informed 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. Patients with aHUS should be informed 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. Patients who discontinue Soliris should be instructed 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.
352 Knotter Drive
Cheshire, CT 06410 USA

US License Number 1743

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

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125166s172

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Acting Division Director
Subject	Division Director Summary Review and CDTL memo
NDA/BLA #	125166/172
Supplement #	
Applicant Name	Alexion Pharmaceuticals, Inc.
Date of Submission	3/25/11
PDUFA Goal Date	9/24/11
Proprietary Name / Established (USAN) Name	Soliris/eculizumab
Dosage Forms / Strength	300 mg single-use vials containing 30 mL of 10 mg/mL sterile, preservative-free Soliris solution per vial. for intravenous infusion
Proposed Indication(s)	Treatment of atypical hemolytic-uremic syndrome
Action/Recommended Action for NME:	Accelerated Approval

Ann. T. Farrell
9/15/11

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Martha Donoghue, M.D.
Statistical Review	Kyung Yul Lee, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	N/A
CMC Review/OBP Review	Lixin Xu, Ph.D. / Chana Fuchs, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Bahru Habtemarian, Ph.D./Julie Bullock, Ph.D.
DDMAC	Adora Ndu
DSI	
CDTL Reviews	Same as this memo
OSE/DMEPA	
OSE/Epidemiology	
OSE/DRISK	
Other - statistical safety	
Other – Consult regarding vaccine prophylaxis	Lucia Lee, M.D., CBER/OVRR/DVRPA

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

Signatory Authority Review Template

1. Introduction

Soliris is a recombinant humanized monoclonal IgG2/4κ antibody that binds to C5 and acts as a complement inhibitor. Soliris was originally approved on March 16, 2007 for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.

On March 25, 2011, Alexion Pharmaceuticals submitted this supplement for the treatment of atypical hemolytic uremic syndrome based on two single arm prospective studies: one study enrolled patients whose disease was responsive to plasma therapy and one study enrolled patients whose disease was not responsive to plasma therapy. The sponsor also submitted a retrospective data collection of patients with atypical hemolytic uremic syndrome (predominantly pediatric) who received Soliris off-label between 2007 and December 2009. The sponsor has ongoing studies for adult and pediatric use in aHUS.

2. Background

Atypical Hemolytic Uremic Syndrome (aHUS) is an extremely rare disease manifested by hemolytic anemia, thrombocytopenia and acute renal failure. aHUS is not caused by *E.coli* producing Shiga toxin but appears to be a genetic disorder associated with mutations and polymorphisms in components and regulators of the complement alternative pathway including factors B, H and I, membrane cofactor protein and C3. For almost all patients, it is a chronic disease. There are no approved therapies for the treatment of atypical hemolytic uremic syndrome. Plasma therapy or plasmapheresis is typically used to manage the disease.

From the executive summary of Dr. Martha Donoghue's primary review:

Atypical hemolytic uremic syndrome (aHUS) is a rare, chronic, life-threatening illness that typically causes irreversible loss of renal function; patients with aHUS often require one or more renal transplants or chronic dialysis. Additionally, patients with aHUS have an increased risk for death and serious thrombotic events such as stroke. There are currently no approved therapies for this disease. No adequate, well-controlled trials have been performed to establish the efficacy of plasma therapy, which is the current standard of care for aHUS.

The mechanism of action for eculizumab is through inhibition of the terminal complement pathway. Binding of eculizumab to the complement protein C5 prevents cleavage of C5 to C5a and C5b, which in turn prevents the generation of the terminal complement complex C5b-9. Prevention of formation of the terminal complement complex inhibits complement mediated thrombotic microangiopathy (TMA) in patients with aHUS.

3. CMC/Device

The reviewer commented in the review:

For the aHUS indication, the new assay, an electro-chemiluminescence (ECL) bridging assay using the whole molecular as target was used. In patients with aHUS treated with Soliris, antibodies to Soliris were detected in 1 of 37 (2.7%) by the ECL assay during the two clinical studies C08-002 A/B and C08-003 A/B. An ECL based neutralizing HAHA assay was also performed in all 37 patients with aHUS in the two clinical trials for detection of neutralizing antibodies. No neutralizing activity to Soliris was detected in patients with aHUS treated with Soliris. It should be noted that this neutralizing assay has poor sensitivity based on the validation data that was reviewed under Submission STN 125166/ (b) (4) for PMC#5 (To develop a validated and sensitive assay for the measurement of neutralizing HAHA to eculizumab. Alternatively, Alexion commits to submit documentation to FDA demonstrating with due diligence that a suitable assay could not be feasibly developed and that the assessment of serum lactate dehydrogenase (LDH) is a sufficiently sensitive indicator of the presence of neutralizing antibodies. This information will be submitted to the BIA by July 9, 2008). This PMC was considered to be fulfilled by FDA on August 25, 2011.

Review of the immunogenicity data resulted in labeling revision. The Environmental Assessment calculation was acceptable.

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

There are no issues that would preclude approval of this supplement. However the review team recommends that the sponsor submit PK and efficacy data from the ongoing pediatric clinical trial and update the population PK model using data from the ongoing pediatric trial.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

From Dr. Martha Donoghue's review:

Two prospective single arm studies (Study C08-002 A/B and Study C08-003 A/B) and one retrospective study (C09-001r) evaluated the safety and efficacy of eculizumab for the treatment of aHUS.

- Study C08-002 studied the effect of eculizumab therapy in patients with aHUS who displayed signs of thrombotic microangiopathy (TMA) despite receiving at least four plasma therapy (PT) treatments the week prior to screening. Sixteen adults and one adolescent patient enrolled in this trial.
- Study C08-003 studied eculizumab in patients with aHUS undergoing chronic plasma therapy (PT) 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. Fifteen adults and five adolescent patients enrolled in this trial.
- Study C09-001r was a retrospective study of patients who received eculizumab outside of an Alexion-sponsored trial for the treatment of aHUS between 2007 and December 2009. Nineteen children and eleven adults enrolled in this trial.

All three studies evaluated the effect of eculizumab therapy on several endpoints related to thrombotic microangiopathy (TMA). 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 intervention rate (defined as the number of plasma therapy interventions and new or increased frequency of dialyses required per patient per day).

The major regulatory endpoint of interest is improvement in renal function. As noted by Dr. Donoghue:

Therefore, analysis of improvement in renal function conferred by eculizumab, as evidenced by decrease in requirement for dialysis, provides the most concrete evidence that eculizumab provides clinical benefit to patients. Improvements in estimated glomerular filtration rate (eGFR) provide supportive evidence that eculizumab mitigates or improves acute renal damage caused by thrombotic microangiopathy in aHUS. Analysis of other descriptive endpoints, including hematologic normalization, platelet count change from baseline, TMA event-free status, and TMA-intervention rates provide additional supportive evidence of an effect on eculizumab therapy on markers of thrombotic microangiopathy.

From the executive summary of Dr. Martha Donoghue's primary review:

The United States Food and Drug Administration (FDA), Division of Hematology Products (DHP) clinical review team recommends that the following regulatory actions be taken for sBLA 125166:

- Approval of Soliris (eculizumab) for the treatment of adult patients with atypical hemolytic uremic syndrome (aHUS)
- Accelerated approval of Soliris (eculizumab) for the treatment of pediatric patients with atypical hemolytic uremic syndrome (aHUS).

Atypical hemolytic uremic syndrome (aHUS) is a rare, chronic, life-threatening illness that typically causes irreversible loss of renal function; patients with aHUS often require one or more renal transplants or chronic dialysis. Additionally, patients with aHUS have an increased risk for death and serious thrombotic events such as stroke. There are currently no approved therapies for this disease. No adequate, well-controlled trials have been performed to establish the efficacy of plasma therapy, which is the current standard of care for aHUS.

The approval of eculizumab for the treatment of adult patients with aHUS is based upon data from two prospective single arm studies demonstrating a favorable treatment effect on renal function and thrombotic microangiopathy (TMA) in a total of 37 adult and adolescent patients.

In Study C08-002, elimination of the requirement for dialysis, sustained improvement in estimated glomerular filtration rate (eGFR) , and sustained improvement in hematologic parameters were observed in patients with plasma therapy-resistant aHUS. Four of the five patients who required dialysis at study entry were able to discontinue dialysis for the duration of Soliris treatment. Additionally, a median improvement in estimated eGFR of at least 15 ml/min/1.73 m² was observed in 9 of 17 (53%) patients enrolled for a median duration of 251 days (range 28-392 days). Hematologic normalization, defined as achievement or maintenance of normal platelet counts and LDH levels for at least four weeks, was achieved in 13 of 17 (76%) patients for a median duration of 37 weeks (range: 25, 62 weeks). These findings are supported by an elimination of the requirement for plasma therapy in the majority of patients, as well as improvement in other laboratory markers of hemolysis and almost complete suppression of terminal complement activity.

In Study C08-003, maintenance of renal function and sustained maintenance of normal hematologic parameters were observed in patients with aHUS who required chronic plasma therapy prior to enrollment. In Study C08-003, hematologic normalization, reflecting maintenance of normal platelet counts and LDH parameters after discontinuation of chronic plasma therapy, occurred in 18 of 20 (90%) of patients. The median duration of hematologic normalization was 38 weeks (range: 22 to 52 weeks). These findings are supported by maintenance of stable parameters of

renal function and absence of a new dialysis requirement in patients who received long-term plasma therapy prior to treatment with eculizumab.

The clinical review team recommends that eculizumab be granted Subpart E (accelerated) approval under 21 CFR 601.41 for the treatment of pediatric patients with aHUS. This regulatory recommendation is applicable under 21 CFR 601.40. This subpart applies to "certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)." These regulations also state that "Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit."

Accelerated approval for eculizumab in the treatment of pediatric patients with aHUS is based upon data from a single retrospective study, C09-001r. The outcomes of the 19 pediatric patients enrolled in Study C09-001r were consistent with the outcomes observed in adult and adolescent patients enrolled in the prospective studies. In Study C09-001r, four of eight (50%) pediatric patients who previously required dialysis were able to discontinue dialysis after starting eculizumab therapy. Additionally, 7 of 19 (37%) pediatric patients exhibited an improvement in eGFR of at least $15 \text{ mg/min}1.73 \text{ m}^2$, and 8 of 19 (42%) of pediatric patients achieved or maintained normal hematologic parameters for at least four weeks. These findings are supported by an elimination of the requirement for plasma therapy in the majority of patients enrolled in Study C09-001r. Finally, because pediatric and adult aHUS share a common pathophysiology, the efficacy of eculizumab in pediatric aHUS is supported by the evidence of effectiveness demonstrated in adult and adolescent patients enrolled in Studies C08-002 and C08-003.

*The review team acknowledges the limitations inherent in relying on results from single arm studies in a small number of patients to support approval. However, the Agency's procedures outlined in subpart E of 21 CFR part 312, which expedite the development, evaluation, and marketing of promising therapies to treat individuals with life-threatening and severely debilitating illnesses, reflect that the Agency must make a medical risk-benefit judgment in deciding whether to approve a drug or biological product. As part of this risk-benefit analysis, the Agency will take "into consideration the severity of the disease and the absence of satisfactory alternative therapy" (21 CFR 312.84). Due to the rarity of atypical hemolytic uremic syndrome, it is not feasible to conduct a randomized controlled trial to evaluate therapy for this disease. Plasma therapy has evolved as the current standard of care for aHUS based upon expert opinion from historical anecdotal experience, rather than evidence from well controlled studies. Furthermore, although plasma therapy may be beneficial to some patients with aHUS, a large subset of patients progress to end stage renal failure or die within one year of diagnosis (Loirat C et al. 2008 *Pediatr Nephrol*). Therefore, taking into consideration the challenges of studying treatments for aHUS, the life-threatening nature of aHUS, and the absence of satisfactory, approved*

alternative therapy, the clinical review team concluded that the totality of data in this submission provide sufficient evidence to grant regular approval for the treatment of adult patients with aHUS, and accelerated approval for the treatment of pediatric patients with aHUS.

The clinical team recommended several postmarketing requirements to confirm clinical benefit in pediatric patients, and gather more comprehensive safety and efficacy data to better inform patients and healthcare providers of the risks and benefits of eculizumab therapy for atypical hemolytic uremic syndrome. Section 1.4 provides details of these proposed PMRs.

I have read Dr. Donoghue's review. In addition to improvements in eGFR noted in the studies, four out of five patients requiring dialysis within one week of starting eculizumab in Study C08-002 were able to discontinue dialysis. These results suggest clinical benefit. An additional four out of eight pediatric patients in C09-001r were also able to discontinue dialysis.

Although these results are encouraging, there are two trials in patients with aHUS that are still ongoing. One trial is enrolling adult patients, C10-004, entitled "An open-label, multi-center clinical trial of eculizumab in adult patients with atypical hemolytic uremic syndrome." The other is a trial enrolling pediatric patients, C10-003, entitled "An open-label, multi-center clinical trial of eculizumab in pediatric patients with atypical hemolytic uremic syndrome." Completion of these studies and submission of the final study report and accompanying datasets will be required before the Agency grants regular approval.

Because the studies submitted to support this sBLA enrolled only patients with aHUS, there is no evidence that Soliris is safe and effective in the treatment of the more common form of hemolytic uremic syndrome, which is usually associated with a diarrheal illness caused by a strain of *E.coli* that produces Shiga toxin. This information should be in labeling to avoid confusion.

8. Safety

From Dr. Donoghue's primary review:

*The most serious adverse event associated with eculizumab therapy is infections caused by *Neisseria meningitidis*. The increased risk of this infection is due to its mechanism of action. In binding complement protein C5, eculizumab prevents the formation of terminal complement complex C5b-9, which is an integral component of host defense against *Neisseria meningitidis*. As of June 30, 2011, there have been 23 cases of *N. meningitidis* infections in patients treated with eculizumab, including four cases resulting in death. A risk evaluation and mitigation strategy is currently in place to mitigate patient risk (please see Section 1.3 for details). To date, one patient with aHUS has developed a *N. meningitidis* infection.*

In her review, she further states:

The most frequently reported adverse reactions in the two prospective aHUS trials (> 15% combined per patient incidence) are hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection and leukopenia. A total of 20 of 37 (54%) patients enrolled in the two prospective aHUS trials experienced serious adverse events (SAE). It is likely that many of these SAEs were not directly related to eculizumab, because the patient population in these studies were predisposed to developing the most commonly reported SAEs, hypertension (16%) and infections (14%). All hypertensive SAEs occurred in patients with a preexisting history of hypertension, and 3 of the 5 patients who incurred infectious SAEs received concomitant immunosuppressive medications for the prevention of renal transplant rejection. All of the infectious SAEs resolved with appropriate therapy.

Despite the relative large percentage of SAEs, 86% (32/37) of patients in the prospective studies decided to continue treatment with eculizumab after completion of the initial 26 week therapy period. In Study C08-002, 13 of 17 (76%) patients elected to continue eculizumab after completing 26 weeks of therapy, and remained on eculizumab at the time of data cut-off. In Study C08-003, 19 of 20 patients continued to receive eculizumab through the data cut-off data; the patient who did not remain on study achieved hematologic normalization and discontinued eculizumab after 26 weeks of treatment, had an aHUS exacerbation 11 weeks later, and was subsequently retreated with commercially available eculizumab. Additionally, only one patient in the two prospective studies was categorized as having discontinued eculizumab due to an adverse event. In this patient, who was on immunosuppressive therapy for prophylaxis of renal allograft rejection, the reasons cited for discontinuation of eculizumab were worsening pancytopenia and renal function, which arguably constitute lack of efficacy rather than true adverse events.

The adverse event profile in pediatric patients enrolled in Study C09-001r was similar to that observed in adult and adolescent patients enrolled in the prospective studies, with the exception of adverse events that are often observed more frequently in children. Pyrexia (9/19, or 47%), cough (5/19, or 26%), upper respiratory tract infection (5/19, or 26%), nasal congestion (4/21%), and tachycardia (4/21%) occurred in more than two pediatric patients at an incidence at least 5% greater than that seen in adults and adolescents in the prospective studies. Serious adverse events were reported in a total of 4 of 19 (21%) pediatric patients. The most common serious adverse events in pediatric patients were infections, which included a central line infection, streptococcal pneumonia, peritonitis, a respiratory tract infection, an upper respiratory tract infection and a fungal infection. All infections resolved with appropriate therapy, and all patients who had infectious SAEs remained on eculizumab. Two patients died in Study C09-001r, including 1 pediatric patient. However, it is unlikely that either death was related to eculizumab (see Section 7.3.1 of this review for details).

The evaluation of safety in this application was challenging due to the small numbers of patients, the lack of a comparator arm, the presence of multiple comorbid medical conditions requiring concomitant therapy, and the heterogeneity of the patient population enrolled in the trials submitted to support this application. The retrospective design of Study C09-001r further complicated the analysis of safety in the pediatric population. However, the safety database provided by the postmarketing experience of eculizumab in the PNH population provided additional supportive safety information to facilitate an adequate risk/benefit analysis in this sBLA.

In summary, the safety profile of eculizumab in adult and pediatric patients with aHUS appears to be comparable to the safety profile that has been observed in patients treated with paroxysmal nocturnal hemoglobinuria (PNH). In clinical studies, patients with aHUS had a higher incidence of adverse events related to renal impairment, such as hypertension, but it is likely that these adverse events are related to aHUS, rather than eculizumab. Additionally, a higher incidence of serious adverse events was reported in aHUS clinical studies compared to PNH clinical studies. However, patients in aHUS clinical studies were generally burdened with more underlying comorbidities prior to enrollment, compared to patients enrolled in the PNH studies. Furthermore, the fact that the majority of patients elected to remain on eculizumab therapy at the time of data cut-strongly supports that the risk/benefit profile favors treatment in patients with aHUS. Therefore, after careful review and analysis of the totality of the data submitted to support this sBLA, the clinical review team concluded that eculizumab has an acceptable risk/benefit profile for patients with atypical hemolytic uremic syndrome, a life-threatening disease. The clinical team proposed postmarketing requirements to further characterize the safety of eculizumab in pediatric and adult patients with PNH (please see Section 1.4 for details regarding the proposed PMRs).

I have read her review and concur. The co-morbidities and retrospectively collected safety data for use in pediatric patients probably underestimate the frequency of adverse events; therefore information from the ongoing trial in pediatric patients will be necessary for labeling.

9. Advisory Committee Meeting

N/A

10. Pediatrics

The applicant submitted a retrospective collection of data from use of Soliris in the treatment of pediatric patients with aHUS. Due to limitations of the data, this application will receive accelerated approval. The sponsor has an ongoing single arm study of eculizumab in pediatric patients with aHUS.

11. Other Relevant Regulatory Issues

All disciplines provided input for labeling.

DSI inspected five non-US and three US sites. DSI also inspected the records of the applicant. The study and data were found to be reliable.

There are no other unresolved relevant regulatory issues.

12. Labeling

The labeling was reviewed by all review disciplines and consultant staff.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Accelerated Approval of Soliris (eculizumab) for the treatment of adult patients with atypical hemolytic uremic syndrome (aHUS) – due to the need for additional prospective efficacy and safety data to confirm clinical benefit in adult patients with aHUS.

Accelerated approval of Soliris (eculizumab) for the treatment of pediatric patients with atypical hemolytic uremic syndrome (aHUS) – due to the need for additional prospective efficacy and safety data to confirm clinical benefit in pediatric patients with aHUS.

- Risk Benefit Assessment

The risk benefit assessment suggests that use of eculizumab can be beneficial in improving renal function and enabling some patients to stop dialysis treatment. The major risk is infection due to complement inhibition. To date, most cases of *Neisseria meningitidis* infections occurred in immunized patients and were due to strains resistant to current vaccines.

- Recommendation for Post marketing Risk Management Activities

This product is under a REMS due to the risk of *Neisseria meningitidis* infections with Soliris. Updates made to the labeling, REMS and Med Guide. Continue REMS reporting and post-marketing surveillance.

- Recommendation for other Post marketing Study Requirements/ Commitments

We have asked the applicant:

1. To submit the final study report and datasets for the ongoing trial C10-003, entitled “An open-label, multi-center clinical trial of eculizumab in pediatric patients with atypical hemolytic uremic syndrome.” This study will be amended to include pharmacokinetic, efficacy and safety data from a minimum of 5 patients who are treated with eculizumab in each of the following age cohorts:

- a. 1 month to < 23 months
 - b. 2 to < 5 years
 - c. 5 to 12 years.
2. Submit the final study report and datasets for the ongoing trial C10-004, entitled "An open-label, multi-center clinical trial of eculizumab in adult patients with atypical hemolytic uremic syndrome."
 3. Develop and implement a registry to collect data to further characterize the long term efficacy of eculizumab for the treatment of atypical hemolytic uremic syndrome (aHUS). The following data will be collected for a time period of no less than five years for each patients receiving eculizumab for the treatment aHUS:
 - a. Patient death (yes/no)
 - b. Stroke (yes/no)
 - c. Requirement for renal transplant (yes/no)
 - d. New dialysis requirement or increase in the frequency of dialysis (yes/no)
 - e. aHUS exacerbation requiring plasma therapy (yes/no)
 - f. Discontinuation of eculizumab (yes/no) and, if discontinued, the reason for discontinuation.
 4. To evaluate long-term safety of eculizumab in patients with aHUS by analyzing outcomes in the Soliris Safety Registry for a period of no less than five years. At the end of the five year period, submit a final study report to the BLA that describes the major safety findings from this registry, including the specific items listed below, and propose labeling changes as appropriate. The following data will be collected for each patient receiving eculizumab for the treatment aHUS:
 - a. Serious infections, defined as infections necessitating or prolonging hospitalization, or resulting in death. Alexion will collect follow-up information from these patients to assess the nature of the serious infection, the major features of the clinical course, and the survival status. Expedited reporting (15 day telephone or facsimile Medwatch communication) will be provided for the occurrence of these serious infections.
 - b. Malignancy, including the nature of the malignancy and the survival status of patients who develop a malignancy.
 - c. Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among babies born to women exposed to eculizumab during the pregnancy.

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APPLICATION NUMBER:

125166s172

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: BLA 125166/172

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

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APPLICATION NUMBER:

125166s172

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type Supplemental BLA
Application Number(s) 125166
Priority or Standard Priority

Submit Date(s) March 25, 2011
Received Date(s) March 25, 2011
PDUFA Goal Date September 24, 2011
Division / Office Division of Hematology
Products/Office of Oncology
Drug Products

Reviewer Name(s) Martha Donoghue, M.D. *Martha Donoghue 8/31/11*
Clinical Team Leader Ann T. Farrell, M.D. *Ann T. Farrell MD 8/31/11*
Review Completion Date August 31, 2011

Established Name eculizumab
(Proposed) Trade Name Soliris
Therapeutic Class Biologic
Applicant Alexion Pharmaceuticals
Formulation(s) Humanized Monoclonal
Antibody
Dosing Regimen Adults and Pediatric Patients
Weighing ≥ 40 kg: 900 mg IV
every 7 days for the first 4
weeks, followed by 1200 mg IV
7 days later, then 1200 mg IV
every 14 days thereafter.

(See label for weight-based dosing for pediatric patients weighing 5 to < 40 kg)

Indication(s)	Treatment of Adult and Pediatric Patients with Atypical Hemolytic Uremic Syndrome
Intended Population(s)	Pediatric and Adult Patients with Hemolytic Uremic Syndrome

Template Version: March 6, 2009

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1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

The United States Food and Drug Administration (FDA), Division of Hematology Products (DHP) clinical review team recommends that the following regulatory actions be taken for sBLA 125166:

- Approval of Soliris (eculizumab) for the treatment of adult patients with atypical hemolytic uremic syndrome (aHUS)
- Accelerated approval of Soliris (eculizumab) for the treatment of pediatric patients with atypical hemolytic uremic syndrome (aHUS).

Atypical hemolytic uremic syndrome (aHUS) is a rare, chronic, life-threatening illness that typically causes irreversible loss of renal function; patients with aHUS often require one or more renal transplants or chronic dialysis. Additionally, patients with aHUS have an increased risk for death and serious thrombotic events such as stroke. There are currently no approved therapies for this disease. No adequate, well-controlled trials have been performed to establish the efficacy of plasma therapy, which is the current standard of care for aHUS.

The approval of eculizumab for the treatment of adult patients with aHUS is based upon data from two prospective single arm studies demonstrating a favorable treatment effect on renal function and thrombotic microangiopathy (TMA) in a total of 37 adult and adolescent patients.

In Study C08-002, elimination of the requirement for dialysis, sustained improvement in estimated glomerular filtration rate (eGFR), and sustained improvement in hematologic parameters were observed in patients with plasma therapy-resistant aHUS. Four of the five patients who required dialysis at study entry were able to discontinue dialysis for the duration of Soliris treatment. Additionally, a median improvement in estimated eGFR of at least 15 ml/min/1.73 m² was observed in 9 of 17 (53%) patients enrolled for a median duration of 251 days (range 28-392 days). Hematologic normalization, defined as achievement or maintenance of normal platelet counts and LDH levels for at least four weeks, was achieved in 13 of 17 (76%) patients for a median duration of 37 weeks (range: 25, 62 weeks). These findings are supported by an elimination of the requirement for plasma therapy in the majority of patients, as well as improvement in other laboratory markers of hemolysis and almost complete suppression of terminal complement activity.

In Study C08-003, maintenance of renal function and sustained maintenance of normal hematologic parameters were observed in patients with aHUS who required chronic plasma therapy prior to enrollment. In Study C08-003, hematologic normalization, reflecting maintenance of normal platelet counts and LDH parameters after discontinuation of chronic plasma therapy, occurred in 18 of 20 (90%) of patients. The median duration of hematologic normalization was 38 weeks (range: 22 to 52 weeks). These findings are supported by maintenance of stable parameters of renal function and absence of a new dialysis requirement in patients who received long-term plasma therapy prior to treatment with eculizumab.

The clinical review team recommends that eculizumab be granted Subpart E (accelerated) approval under 21 CFR 601.41 for the treatment of pediatric patients with aHUS. This regulatory recommendation is applicable under 21 CFR 601.40. This **subpart applies to "certain biological products** that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient **response over available therapy**)." **These regulations also state that** *"Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit."*

Accelerated approval for eculizumab in the treatment of pediatric patients with aHUS is based upon data from a single retrospective study, C09-001r. The outcomes of the 19 pediatric patients enrolled in Study C09-001r were consistent with the outcomes observed in adult and adolescent patients enrolled in the prospective studies. In Study C09-001r, four of eight (50%) pediatric patients who previously required dialysis were able to discontinue dialysis after starting eculizumab therapy. Additionally, 7 of 19 (37%) pediatric patients exhibited an improvement in eGFR of at least $15 \text{ mg/min}1.73 \text{ m}^2$, and 8 of 19 (42%) of pediatric patients achieved or maintained normal hematologic parameters for at least four weeks. These findings are supported by an elimination of the requirement for plasma therapy in the majority of patients enrolled in Study C09-001r. Finally, because pediatric and adult aHUS share a common pathophysiology, the efficacy of eculizumab in pediatric aHUS is supported by the evidence of effectiveness demonstrated in adult and adolescent patients enrolled in Studies C08-002 and C08-003.

The review team acknowledges the limitations inherent in relying on results from single arm studies in a small number of patients to support approval. However, the Agency's procedures outlined in Subpart E of 21 CFR part 312, which expedite the development, evaluation, and marketing of promising therapies to treat individuals with life-threatening and severely debilitating illnesses, reflect that the Agency must make a medical risk-benefit judgment in deciding whether to approve a drug or biological product. As part of this risk-benefit analysis, the Agency will take "into consideration the severity of the disease and the absence of satisfactory **alternative therapy**" (21 CFR

312.84). Due to the rarity of atypical hemolytic uremic syndrome, it is not feasible to conduct a randomized controlled trial to evaluate therapy for this disease. Plasma therapy has evolved as the current standard of care for aHUS based upon expert opinion from historical anecdotal experience, rather than evidence from well controlled studies. Furthermore, although plasma therapy may be beneficial to some patients with aHUS, a large subset of patients progress to end stage renal failure or die within one year of diagnosis (Loirat C et al. 2008 *Pediatr Nephrol*). Therefore, taking into consideration the challenges of studying treatments for aHUS, the life-threatening nature of aHUS, and the absence of satisfactory, approved alternative therapy, the clinical review team concluded that the totality of data in this submission provide sufficient evidence to grant regular approval for the treatment of adult patients with aHUS, and accelerated approval for the treatment of pediatric patients with aHUS.

The clinical team recommended several postmarketing requirements to confirm clinical benefit in pediatric patients and to gather more comprehensive safety and efficacy data to better inform patients and healthcare providers of the risks and benefits of eculizumab therapy for atypical hemolytic uremic syndrome. Section 1.4 provides details of these proposed PMRs.

1.2 Risk Benefit Assessment

This submission provided safety data from 67 patients treated with eculizumab in aHUS clinical trials. Additionally, at the time of submission of this sBLA, the cumulative post-marketing exposure to Soliris was estimated to be approximately 2030 patient years, primarily in patients with paroxysmal nocturnal hemoglobinuria.

The most serious adverse event associated with eculizumab therapy is infections caused by *Neisseria meningitidis*. The increased risk of this infection is due to its mechanism of action. In binding complement protein C5, eculizumab prevents the formation of terminal complement complex C5b-9, which is an integral component of host defense against *Neisseria meningitidis*. As of June 30, 2011, there have been 23 cases of *N. meningitidis* infections in patients treated with eculizumab, including four cases resulting in death. A risk evaluation and mitigation strategy is currently in place to mitigate patient risk (please see Section 1.3 for details). To date, one patient with aHUS has developed a *N. meningitidis* infection.

Because of its mechanism of action, current labeling also includes a warning that eculizumab may increase the risk of developing other serious infections, particularly from other encapsulated organisms. Although there are numerous postmarketing reports of patients developing various infections while receiving eculizumab, these infections generally occurred in patients who have an underlying predisposition for developing of infections due to factors such as comorbid medical conditions that adversely affect immune function, concomitant immunosuppressive therapy, or the presence of central venous catheters. Therefore, there is insufficient evidence at this

time to establish that eculizumab plays a causal role in the development of serious infections other than *N. meningitidis*. Nevertheless, there is a theoretical potential for an increased risk for the development of serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in vulnerable pediatric patients, especially those less than 5 years of age. Because only eight patients below the age of five years have been treated with eculizumab to date, it is not possible to determine if this risk is solely theoretical. Therefore, the proposed labeling continues to include a warning that eculizumab may increase the risk for the development of serious infections due to other encapsulated organisms. In addition, the label includes instructions for pediatric patients to promptly receive immunization for prevention of *S. pneumoniae* and *H. influenzae* infections according to current guidelines from the American Council on Immunization Practices (ACIP).

The most frequently reported adverse reactions in the two prospective aHUS trials (> 15% combined per patient incidence) are hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection and leukopenia. A total of 20 of 37 (54%) patients enrolled in the two prospective aHUS trials experienced serious adverse events (SAE). It is likely that many of these SAEs were not directly related to eculizumab, because the patient population in these studies were predisposed to developing the most commonly reported SAEs, hypertension (16%) and infections (14%). All hypertensive SAEs occurred in patients with a preexisting history of hypertension, and 3 of the 5 patients who incurred infectious SAES received concomitant immunosuppressive medications for the prevention of renal transplant rejection. All of the infectious SAEs resolved with appropriate therapy.

Despite the relative large percentage of SAEs, 86% (32/37) of patients in the prospective studies decided to continue treatment with eculizumab after completion of the initial 26 week therapy period. In Study C08-002, 13 of 17 (76%) patients elected to continue eculizumab after completing 26 weeks of therapy, and remained on eculizumab at the time of data cut-off. In Study C08-003, 19 of 20 patients continued to receive eculizumab through the data cut-off data; the patient who did not remain on study achieved hematologic normalization and discontinued eculizumab after 26 weeks of treatment, had an aHUS exacerbation 11 weeks later, and was subsequently retreated with commercially available eculizumab. Additionally, only one patient in the two prospective studies was categorized as having discontinued eculizumab due to an adverse event. In this patient, who was on immunosuppressive therapy for prophylaxis of renal allograft rejection, the reasons cited for discontinuation of eculizumab were worsening pancytopenia and renal function, which arguably constitute lack of efficacy rather than true adverse events.

The adverse event profile in pediatric patients enrolled in Study C09-001r was similar to that observed in adult and adolescent patients enrolled in the prospective studies, with the exception of adverse events that are often observed more frequently in children. Pyrexia (9/19, or 47%), cough (5/19, or 26%), upper respiratory tract infection (5/19, or

26%), nasal congestion (4/21%), and tachycardia (4/21%) occurred in more than two pediatric patients at an incidence at least 5% greater than that seen in adults and adolescents in the prospective studies. Serious adverse events were reported in a total of 4 of 19 (21%) pediatric patients. The most common serious adverse events in pediatric patients were infections, which included a central line infection, streptococcal pneumonia, peritonitis, a respiratory tract infection, an upper respiratory tract infection and a fungal infection. All infections resolved with appropriate therapy, and all patients who had infectious SAEs remained on eculizumab. Two patients died in Study C09-001r, including 1 pediatric patient. However, it is unlikely that either death was related to eculizumab (see Section 7.3.1 of this review for details).

The evaluation of safety in this application was challenging due to the small numbers of patients, the lack of a comparator arm, the presence of multiple comorbid medical conditions requiring concomitant therapy, and the heterogeneity of the patient population enrolled in the trials submitted to support this application. The retrospective design of Study C09-001r further complicated the analysis of safety in the pediatric population. However, the safety database provided by the postmarketing experience of eculizumab in the PNH population provided additional supportive safety information to facilitate an adequate risk/benefit analysis in this sBLA.

In summary, the safety profile of eculizumab in adult and pediatric patients with aHUS appears to be comparable to the safety profile that has been observed in patients treated with paroxysmal nocturnal hemoglobinuria (PNH). In clinical studies, patients with aHUS had a higher incidence of adverse events related to renal impairment, such as hypertension, but it is likely that these adverse events are related to aHUS, rather than eculizumab. Additionally, a higher incidence of serious adverse events was reported in aHUS clinical studies compared to PNH clinical studies. However, patients in aHUS clinical studies were generally burdened with more underlying comorbidities prior to enrollment, compared to patients enrolled in the PNH studies. Furthermore, the fact that the majority of patients elected to remain on eculizumab therapy at the time of data cut-off strongly supports that the risk/benefit profile favors treatment in patients with aHUS. Therefore, after careful review and analysis of the totality of the data submitted to support this sBLA, the clinical review team concluded that eculizumab has an acceptable risk/benefit profile for patients with atypical hemolytic uremic syndrome, a life-threatening disease. The clinical team proposed postmarketing requirements to further characterize the safety of eculizumab in pediatric and adult patients with PNH (please see Section 1.4 for details regarding the proposed PMRs).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

In 2007, when Soliris received initial approval for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria, the applicant had instituted risk mitigation measures that were not formally approved by FDA. On June 4, 2010, FDA approved a Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risks and morbidity associated with infection with *Neisseria meningitidis*, other serious infections, and severe hemolysis after eculizumab discontinuation. The REMS consists of the following components:

- A Medication Guide
- Elements to Assure Safe Use
 - Healthcare providers who prescribe Soliris are enrolled in the “OneSource Safety Support Program” by signing an enrollment form that certifies that they will counsel and provide educational materials to patients about the risks of Soliris therapy outlined above.
 - Healthcare providers agree to promptly report cases of meningococcal infection to the applicant and FDA.
- A time table requiring that a REMS assessment be submitted every 6 months for 1 year, then annually.

In this sBLA submission, the applicant included a REMS modification to include the proposed aHUS indication. Aside from the inclusion of the proposed new indication, the elements of the REMS were unchanged. On June 1, 2011, the applicant submitted a REMS assessment report. This report indicated that (b) (4) % of current prescribers are registered in the OneSource Safety Support Program.

After analyzing outcomes of the REMS, postmarketing data, and the REMS assessment report submitted by the sponsor, the DRISK and DHP clinical review teams agreed that the REMS should be modified to focus on the risk of meningococcal infection. On August 22, FDA discussed the following proposed changes to the REMS with the applicant:

- Incorporation of additional ways for prescribers to enroll in the OneSource Safety Support Program (such as online and phone enrollment) in order to facilitate and expedite prescriber enrollment
- Coupling of prescriber enrollment and certification with access to the drug, so that prescribers who do not enroll do not have access to the drug (prescribers who require Soliris for urgent treatment of a patient may acquire the drug on a short term basis without being formally enrolled).

- Removal of mitigation strategies to reduce the risk and morbidity of serious infections from the REMS (because postmarketing data have not supported a link between eculizumab and serious infections other than N. meningitidis, and it is not possible to determine causality with case reports in the population receiving Soliris)
- Removal of mitigation strategies to reduce the risk and morbidity of discontinuation hemolysis from the REMS (because no cases of severe hemolysis in patients with PNH who discontinue eculizumab have been reported in the postmarketing setting).

During this teleconference, Alexion provided a preliminary opinion that the proposed modifications to the REMS appeared reasonable. FDA also proposed several additional modifications to the proposed REMS documents in order to achieve consistency with FDA modifications to the proposed labeling. At the time of completion of this review, REMS modifications have not been finalized.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical team proposed four post market requirements (PMRs) for this application. On August 25, 2011, a teleconference was held with the applicant to discuss the following proposed PMRs.

1. To submit the final study report and datasets for the ongoing trial C10-003, **entitled "An open-label, multi-center clinical trial of eculizumab in pediatric patients with atypical hemolytic uremic syndrome."** **This study will be amended to include pharmacokinetic, efficacy and safety data from a minimum of 5 patients who are treated with eculizumab in each of the following age cohorts:**
 - a. 1 month to < 23 months
 - b. 2 to < 5 years
 - c. 5 to 12 years.

Reviewer comment: The current studies provide sufficient evidence of clinical benefit to support accelerated approval in pediatric patients. This PMR was proposed to confirm clinical benefit and further characterize the efficacy, safety, and pharmacokinetics of eculizumab for the treatment of atypical hemolytic uremic syndrome in pediatric patients.

2. Submit the final study report and datasets for the ongoing trial C10-004, **entitled "An open-label, multi-center clinical trial of eculizumab in adult patients with atypical hemolytic uremic syndrome."**

Reviewer comment: this PMR was proposed to further characterize the safety and efficacy of eculizumab in adults with aHUS. Due to the rarity of aHUS, the three studies submitted with this application enrolled a relatively small number of patients (a total of 67 patients in the three studies combined). It is anticipated that data from this ongoing study will add valuable information regarding the safety and efficacy of eculizumab in this population, and may provide information to better inform labeling.

3. Develop and implement a registry to collect data to further characterize the long term efficacy of eculizumab for the treatment of atypical hemolytic uremic syndrome (aHUS). The following data will be collected for a time period of no less than five years for each patients receiving eculizumab for the treatment aHUS:
 - a. Patient death (yes/no)
 - b. Stroke (yes/no)
 - c. Requirement for renal transplant (yes/no)
 - d. New dialysis requirement or increase in the frequency of dialysis (yes/no)
 - e. aHUS exacerbation requiring plasma therapy (yes/no)
 - f. Discontinuation of eculizumab (yes/no) and, if discontinued, the reason for discontinuation.

Submit periodic reports annually to the BLA. At the end of the five year period, submit a final study report to the BLA that describes the major efficacy findings, including the specific items listed above.

Reviewer comment: The current studies provide sufficient evidence of clinical benefit to support regular approval in adults and accelerated approval in pediatric patients. However, given the complexity and heterogeneity of atypical HUS and the small number of patients with aHUS available to enroll in clinical trials, longer term follow up of all patient outcomes are necessary to better characterize the long-term efficacy of Soliris.

4. To evaluate long-term safety of eculizumab in patients with aHUS by analyzing outcomes in the Soliris Safety Registry for a period of no less than five years. At the end of the five year period, submit a final study report to the BLA that describes the major safety findings from this registry, including the specific items listed below, and propose labeling changes as appropriate. The following data will be collected for each patient receiving eculizumab for the treatment aHUS:
 - a. Serious infections, defined as infections necessitating or prolonging hospitalization, or resulting in death. Alexion will collect follow-up information from these patients to assess the nature of the serious infection, the major features of the clinical course, and the survival status.

- Expedited reporting (15 day telephone or facsimile Medwatch communication) will be provided for the occurrence of these serious infections.
- b. Malignancy, including the nature of the malignancy and the survival status of patients who develop a malignancy.
 - c. Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among babies born to women exposed to eculizumab during the pregnancy.
 - d. Thrombotic events, including the nature of the event, the clinical outcome, as well as the anticoagulant management prior to and after the event.

Reviewer comment: Due to the rarity of atypical hemolytic uremic syndrome and lack of available therapy that has been rigorously studied, conducting a randomized trial to evaluate safety is not feasible. Given the complexity and heterogeneity of atypical HUS and the small number of patients with aHUS available to enroll in clinical trials, longer term follow up of patient outcomes are necessary to better inform patients and physicians about the long-term safety of Soliris. The applicant currently collects safety data, which includes items a-d above, through the Soliris Safety Observation Program. This program is being conducted to satisfy the conditions of the REMS that was required as part of the initial approval of Soliris for the treatment of adult patients with PNH. The Soliris Safety Observation Program systematically collects safety data from all patients who are treated with Soliris, regardless of indication. The applicant will provide periodic reports summarizing the safety data from patients with aHUS that are collected through this registry.

During this teleconference, Alexion provided a preliminary opinion that the following proposed post market requirement appeared reasonable. However, at the time of completion of this review, the content of the PMRs is under negotiation.

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

This submission is an efficacy supplement. For detailed product information, please refer to the original BLA (125166/0) review submitted on March 15, 2007.

Eculizumab is a recombinant humanized IgG2/4 κ monoclonal 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.

The following figure contains a schematic diagram of eculizumab (Source: Sponsor Submission Module 2.5, Original BLA application May 30, 2006).

Figure 1: Schematic Diagram of Eculizumab

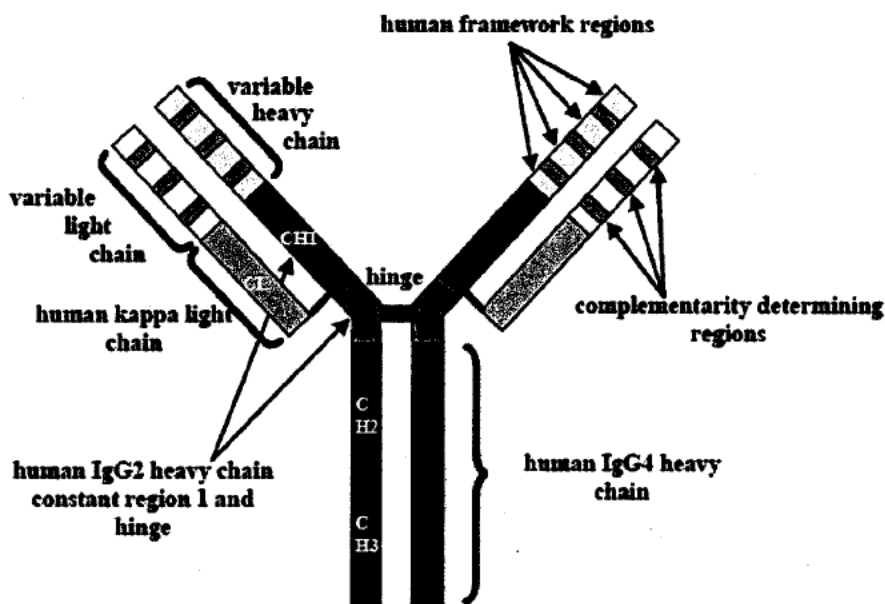
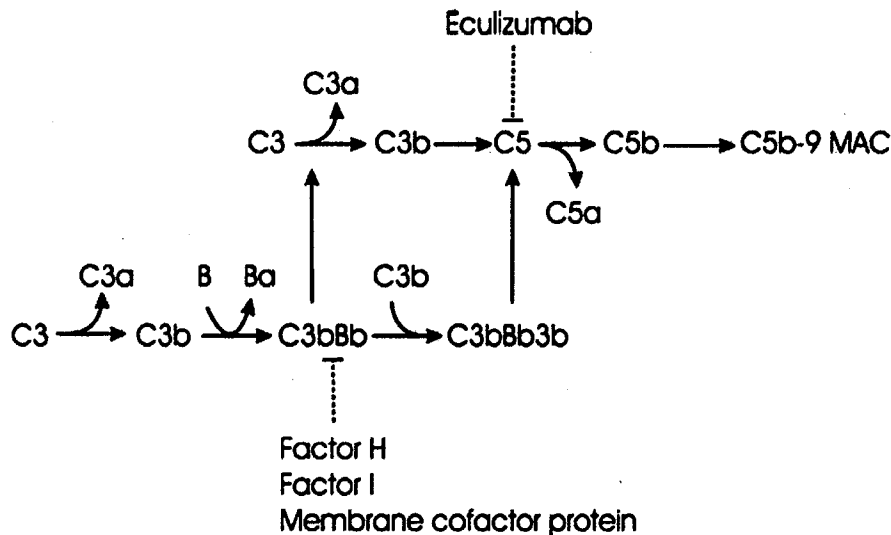


Figure 2 depicts the mechanism of action of eculizumab. Eculizumab binds to the complement protein C5, thereby inhibiting cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9.

Figure 2: The effect of eculizumab on the alternative complement pathway in the treatment of aHUS



Source: Taylor CM et al. 2010 British Journal of Haematology,

FDA approved eculizumab (trade name: Soliris[®]) for the treatment of adult patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) on March 16, 2007. PNH is an acquired genetic deficiency of terminal complement inhibition. PNH evolves from clonal expansion of hematopoietic progenitor cells that harbor a somatic mutation causing loss of the glycosylphosphatidylinositol (GPI)-linked terminal complement inhibitors CD55 and CD59. This loss of inhibition of terminal complement activation results in uncontrolled complement-mediated hemolysis and excessive complement-mediated activation of white blood cells and platelets.

Efficacy data from the TRIUMPH (C 04-001) study provided the primary basis for approval of eculizumab for the treatment of PNH. This study was a randomized, double-blind, placebo-controlled, multicenter, multinational trial conducted in transfusion dependent patients with PNH. The study demonstrated that eculizumab therapy resulted in stabilization of hemoglobin levels and reduction in the requirement for red blood cell transfusions. In addition, the SHEPHERD (C 04-002) study provided supportive evidence of efficacy in this patient population. The SHEPHERD study was an open label, multicenter, multinational trial in which eculizumab decreased intravascular hemolysis as measured by serum lactate dehydrogenase (LDH) levels in patients with PNH.

The approved dosage regimen for treatment of PNH is as follows:

- 600 mg via intravenous infusion over 35 minutes every 7 days for the first 4 weeks, followed by
- 900 mg intravenously 7 days later, then
- (b) (4) mg every 14 days thereafter.

The safety of this regimen was supported by comparative information from the placebo-controlled TRIUMPH study and an analysis of the safety in all PNH patients exposed to eculizumab. The most frequently reported adverse reactions reported in patients treated with eculizumab in PNH clinical trials ($\geq 10\%$ overall and greater than placebo) are: headache, nasopharyngitis, back pain, nausea and diarrhea. Current labeling contains a box warning that Soliris increases the risk of meningococcal infections. This warning provides instructions for vaccination of patients with a meningococcal vaccine at least 2 weeks prior to receipt of the first dose of Soliris, and instructions for revaccination at standard intervals. Additionally, the label includes a warning for the potential of hemolysis in patients with PNH who discontinue eculizumab.

Alexion agreed to a postmarketing commitment to evaluate long-term safety of eculizumab by analyzing patient outcomes in the Soliris Safety Registry for a time period of at least five years. In this registry, PNH patients treated with eculizumab are followed for the occurrence of serious infections, malignancy, thrombotic events, pregnancy-related complications, and congenital abnormalities in babies born to women exposed to eculizumab during pregnancy. Additionally, the safety registry will collect dosage and safety information for pediatric patients treated with eculizumab. A Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide and Elements to Assure Safe Use, is currently in effect to limit the risk of occurrence and morbidity associated with meningococcal infections and impart important safety information to ensure safe and proper use of eculizumab.

2.2 Tables of Currently Available Treatments for Proposed Indications

This sBLA seeks the addition of the following indication for eculizumab:

Soliris is a complement inhibitor indicated for the treatment of patients with atypical hemolytic uremic syndrome.

There are currently no approved therapies for aHUS. Treatment usually includes plasma therapy or plasmapheresis, which is aimed at the transient reduction in abnormal complement regulatory proteins, or autoantibodies to complement regulatory proteins, and restoration of the normal balance of complement activity. There are no well controlled trials evaluating the safety and efficacy of plasma therapy for the treatment of aHUS, but recently published treatment guidelines based upon accumulated experience recommend plasma therapy for the initial treatment of aHUS. (Taylor CM et al. 2010 British Journal of Haematology). Immunosuppressive

medications and supportive care are also employed in the treatment of patients with aHUS. Kidney transplantation is also performed in patients with end stage renal disease; however, one series of 33 patients with aHUS who underwent renal transplantation reported a success rate of only 18%, due to recurrence of disease or thrombosis. (Zimmerhackl L. et al. 2006 Seminars in Thrombosis and Hemostasis)

2.3 Availability of Proposed Active Ingredient in the United States

FDA approved eculizumab (trade name: Soliris®) for the treatment of patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) on March 16, 2007.

2.4 Important Safety Issues With Consideration to Related Drugs

There are currently no pharmacologically related products other than other monoclonal antibodies used for the treatment of a variety of diseases. Hypersensitivity reactions, including infusion reactions, are typically associated with the use of monoclonal antibodies. The potential for development of neutralizing anti-human-antibodies is also a risk of therapy with monoclonal antibodies, such as eculizumab, that have human constant regions.

The primary safety concern identified with the use of Soliris in patients with PNH is the increased risk of meningococcal infections. Current labeling contains a box warning to advise patients and medical caregivers that Soliris increases the risk of meningococcal infections. In addition, the label contains the following additional information in the Warnings and Precautions Section:

- caution is advised when Soliris is administered to patients with systemic infections
- patients who receive Soliris may be at risk for the development of other infections
- patients with paroxysmal nocturnal hemoglobinuria (PNH) should be monitored closely for signs of hemolysis following discontinuation of Soliris
- LDH monitoring may assist in evaluating the effects of Soliris in the treatment of PNH, and that a decrease in the Soliris dosing interval from 14 to 12 days was necessary to achieve a reduction in LDH in six patients with PNH.
- treatment with Soliris should not alter anticoagulation management
- **infusion reactions may occur with Soliris (although they haven't yet been observed).**

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1 summarizes the key regulatory activities relating to this sBLA

Table 1: Key Regulatory Activities for sBLA 125166

Date	Nature of Regulatory Activity	Issues
3/16/2007	Initial BLA approval	• Adult PNH indication granted
4/12/2010	Type C Meeting to discuss the development plan for aHUS	• FDA agreed that the proposed dosing strategy appeared reasonable, but acceptance would be based on review of relevant PK/PD data and modeling. • Alexion agreed to provide a summary and analysis of worldwide experience with the use of eculizumab in pediatric patients with aHUS in the sBLA. • FDA stated "An appropriately designed single-arm trial could be appropriate for this patient population" • FDA informed Alexion that protocols for aHUS studies should include more specific definition and criteria for platelet counts, LDH status, renal function, and hemoglobin levels qualifying patients for study entry and for changes and/or levels that would indicate resolution of aHUS exacerbation. Studies should demonstrate stabilization of LDH and platelet count stabilization should be demonstrated over time. Endpoint should assess the efficacy of the drug over time. • FDA recommended incorporation of markers of improvement in renal function parameters into efficacy assessments of studies • Alexion agreed to provide data for not only 26 weeks, but for the duration of the study that includes follow-up to 2 years.

Date	Nature of Regulatory Activity	Issues
7/29/2010	Pre-sBLA Meeting	• FDA and Alexion agreed that primary endpoints based on platelet count response alone were not adequate to demonstrate efficacy of eculizumab for the treatment of aHUS. • FDA suggested that a composite endpoint of hematological response and plasma-therapy free status may be an appropriate primary endpoint for study C08-003A/B. • Alexion stated that endpoints would be assessed as change from baseline. • Alexion agreed to submit historical control data from the literature. • FDA stated that Alexion should include a justification for the small number of patients enrolled in the studies in the sBLA. • FDA stated that data up to one year is desirable to support eculizumab safety and efficacy for the treatment of aHUS. sBLA submission should include minimum of 6 months follow up for all patients in studies C08-002A/B and C08-003A/B. • Updated REMS required with the sBLA submission.

2.6 Other Relevant Background Information

2.6.1 Background Related to Atypical Hemolytic Uremic Syndrome (aHUS).

The pathophysiology and clinical course of atypical hemolytic uremic syndrome (aHUS) is distinct from the more common form of hemolytic uremic syndrome (HUS). Hemolytic uremic syndrome (HUS) is a heterogeneous hemolytic disorder, defined by triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment caused by thrombotic microangiopathy (TMA). HUS can be caused by an external environmental trigger, an intrinsic inherited risk factor, or a combination of both. Typically, HUS occurs in the setting of a prodromal diarrheal episode. The majority of cases of HUS are associated with strains of E. Coli that produce a Shiga toxin. However, pneumococcal infection and human immunodeficiency virus infections, metastatic cancers, organ and stem cell transplantation, autoimmune diseases or drugs can also trigger HUS. (Hirt-Minkowski Nephron Clin Pract 2010).

Atypical HUS is a form of TMA which typically manifests as a chronic disease punctuated with multiple relapses. Atypical HUS usually occurs in the absence of a triggering diarrheal or other infection caused by shiga toxin-producing bacteria. Atypical HUS (aHUS) is less common than diarrhea-associated HUS, and accounts for only 5-10% of all cases of HUS. (Capriole J et al. *Curr Opin Crit Care* 2005). Atypical HUS is caused by dysregulation of the alternative complement pathway, resulting in uncontrolled complement activation. Many cases of atypical HUS are idiopathic, but an underlying predisposing condition or inciting factor can often be identified in patients with aHUS. A variety of mutations and polymorphisms of genes that encode complement regulatory proteins have been implicated in the pathogenesis of aHUS. The most frequently reported mutations affect the gene encoding complement factor H (CFH) (50-60% of cases), membrane cofactor protein (MCP) (20% of cases) and complement factor I (CFI) (10-15% of cases) (Hirt-Minkowski P et al. 2010 *Nephron Clin Pract*). At least ten mutations in genes encoding complement regulatory proteins have been identified to date; however, gene mutations are identified in only about half of the patients diagnosed with aHUS. Autoantibodies to complement regulatory proteins have also been implicated in the development of aHUS in some patients.

The incidence of aHUS has been poorly characterized. A European HUS registry identified approximately 167 patients who were diagnosed with atypical HUS between 1974 and 2005. Based on these data, the estimated prevalence in children less than eighteen years of age was estimated to be approximately three per million (Zimmerhackl et al. 2006 *Seminars in thrombosis and Hemostasis*). The prevalence in adults is thought to be lower.

The more common form of HUS has a generally more favorable outcome; end stage renal failure is relatively rare and most patients achieve a long-term complete recovery (Loirat C et al *Pediatr Nephrol* 2008). In contrast, patients with atypical HUS have a variable clinical presentation and clinical course, but commonly develop end stage renal disease. In addition, patients with aHUS are at risk for other TMA complications, including seizures, stroke, cardiomyopathy, myocardial infarction, pancreatitis, and vasculopathy, which may lead to premature death.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

This sBLA submission was of adequate quality to enable a comprehensive review to be conducted.

3.2 Compliance with Good Clinical Practices

Study reports for Study C08-002 A/B and Study C08-003 A/B contain the following statement:

The investigators agreed that the study would be conducted according to the principles of the International Conference on Harmonization (ICH) E6 guideline on GCP, the principles of the World Medical Association Declaration of Helsinki and the ICH E11 Guidelines on Clinical Investigation of Medicinal Products in the Pediatric Population for the adolescent segment of this study.

The investigators were to conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

The clinical study report for Study C09-001r states that investigators conducted all aspects of the study in accordance with all national, state, and local laws of the pertinent regulatory authorities. An additional statement indicated that the retrospective study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline. Prior to beginning the trial, investigators obtained an IRB/IEC approved informed consent and informed assent document to provide to the patient or legal guardians. These documents were prepared in compliance with ICH/GCP, the CFR Part 50 of Title 21, or applicable local regulations. A signed ICF was obtained prior to collection of retrospective data, with the exception of two patients: A signed ICF was not required for Patient 044-012; instead, IRB approval was obtained through a HIPAA waiver of the requirement for an informed consent document to obtain information for a retrospective study by an investigator who is directly involved in providing health care to the respective patient. The wife of patient 121-029 signed the ICF because the patient had died.

3.2.1 DSI Inspections

DSI assisted in the evaluation of data integrity for this sBLA. Due to the relatively small number of patients enrolled in the three studies supporting a new indication for the treatment of a rare disease, and because a retrospective study of a small number of pediatric patients supported the proposed pediatric indication, the clinical reviewer considered it especially important to verify the integrity of the data supporting this application. Sites were chosen primarily based upon the number of patients enrolled, physical proximity to each other, and age range of patients enrolled. DSI inspected five non-US and three US sites. DSI also inspected the records of the applicant. Table 2 shows the sites selected for inspection, and preliminary inspection results.

Clinical Review
 Martha Donoghue
 sBLA 125166
 Soliris (eculizumab)

Table 2: Clinical Sites Inspected During Review of sBLA 125166

Site	Protocol ID	Number of Subjects	Preliminary Inspection Results
Site 198: Christopher Legendre -- Hôpital Necker-Enfants Malades, Service de Transplantation Rénale adulte et Soins Intensifs	C08-002, C08-003	5 of 37 (13%) subjects in both studies combined	No action indicated
Site 197: Yahsou Delmas - CHU Pellegrin, Département de Néphrologie, Unité d'hémodialyse	C08-002, C08-003	3 of 37 (8%) subjects in both studies combined	No action indicated
Site 196: Maryvonne Hourmant - Hôtel Dieu-CHU de Nantes, Service de, Néphrologie et d'Immunologie Clinique	C08-002, C08-003	3 of 37 (8%) subjects in both studies combined	No action indicated
Site 191: Veronique Baudouin - Hôpital Robert Debrém, Service Néphrologie	C09-001r	1 of 30 (3%) subjects	No action indicated
Site 192: Mary Alice Macher - AP-DP Hôpital Robert Debré, Service Néphrologie	C09-001r	1 of 30 (3%) subjects	No action indicated

Site	Protocol ID	Number of Subjects	Preliminary Inspection Results
Site 015: Jodi Smith - Seattle Children's	C09-001r	1 of 30 (3%) subjects	No action indicated; however, a Form 483 was issued for inspectional observations relating to transcriptional errors between the source records and CRFs, and missing laboratory data in CRFs that were present in source documents. <i>Reviewer comment: review of the inspector's descriptions of the missing data and transcriptional errors did not uncover a systematic bias in the errors. None of the errors in data collection resulted in a misrepresentation of the main efficacy and safety outcomes for this patient.</i>
Site 013 – Julius Sherwinter Children's Healthcare of Atlanta, Children's Kidney Center	C09-001r	1 of 30 (3%) subjects	No action indicated
Site 022 – Ralph Gruppo Cincinnati Children's Hospital, Division of Hematology & Oncology	C09-001r	1 of 30 (3%) subjects	No action indicated

Based on the review of preliminary results from inspections of the study conduct of eight clinical investigators and the study sponsor, DSI concluded that the study data collected appear reliable. After conducting an inspection of the applicant, DSI concluded that the conduct and monitoring for both prospective studies appeared adequate. However, DSI concluded that there appeared to be a systematic lack of adequate monitoring by the applicant of the retrieval and transcription of source data from the sites in the retrospective study. DSI noted that the deficiencies noted for Site 015 were attributable to inadequate monitoring of data collection and transcription by the applicant, and not due to site-specific issue. However, DSI concluded that in spite of the applicant's failure to adequately monitor the process of data collection in the retrospective study, "the key

efficacy and safety data generated for all of the subjects (5 of 30, or 18%) audited during FDA inspections were found to be reliable based on review of source records at **the inspected clinical sites.**"

Final results of DSI inspection were pending at the time of completion of this review. Please see the final DSI review for details regarding DSI inspection results, conclusions, and recommendations.

3.2.2 Protocol Violations

Table 3 lists important protocol deviations identified in Study C08-002. A review of Study C08-002, conducted by the applicant, revealed that 5 of 17 subjects did not meet eligibility criteria. Subject 2-043-001 was diagnosed with systemic lupus erythematosus approximately one week following receipt of the first eculizumab dose; this subject subsequently withdrew from the study. One patient had only one screening platelet count collected, and another patient had an average screening platelet count of $108 \times 10^9/L$ (compared to the maximum permitted average screening platelet count of $100 \times 10^9/L$). An additional patient had not received the required minimum number of plasma therapy treatments in the week prior to screening due to a history of a plasma therapy allergy. Finally, another patient had received one dose of eculizumab more than a year prior to study entrance.

Table 3: Tabular Listing of Important Protocol Deviations in Study C08-002

Site	Patient	Deviation Type	Deviation
043	001	Eligibility Criteria	Diagnosed with SLE one week after first eculizumab dose administered
110	001	Eligibility Criteria	One screening platelet count collected
198	001	Eligibility Criteria	Average screening platelet count too high: 108×10^9
197	001	Eligibility Criteria	Did not receive required minimum number of PT treatments prior to screening due to allergy
140	001	Eligibility Criteria	Received one dose of eculizumab > 1 year prior to study entry

Reviewer comment: With the exception of the protocol deviation for patient 043-001, who was expeditiously removed from Study C08-002, the remaining protocol deviations were minor and are not likely to materially impair the interpretation of the study results.

Table 4 lists protocol deviations identified in Study C08-003.

Table 4: Tabular Listing of Protocol Deviations in Study C08-003

Site	Patient	Deviation Type	Deviation
167	001	Eligibility Criteria	One platelet count collected at baseline instead of two
196	001	Eligibility Criteria	One screening platelet count collected
198	001	Eligibility Criteria	One screening platelet count collected – the second clotted
250	003	Eligibility Criteria	Did not have an average platelet count at baseline that was within 75% of the average platelet count at screening (<i>platelet count on Day 0 was approximately 60% of Day 7 platelet count, but was above the upper limit of normal and LDH, hemoglobin and creatinine parameters were stable</i>).

Reviewer comment: The protocol deviations were minor and are not likely to materially impair the interpretation of the study results.

3.3 Financial Disclosures

Alexion submitted Financial Certification and Disclosure Forms for all investigators in Study C08-002 A/B, Study C08-003 A/B, and Study C09-001r. All investigators signed a statement that they had no financial conflicts of interest as defined in 21 CFR 54.1-54.6.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

This section summarizes issues relating to the safety and efficacy of eculizumab identified by other review disciplines as of August 16, 2011. This summary should be considered partial and preliminary. Please refer to the respective discipline reviews for a full description of the issues identified during the course of the review process.

4.1 Chemistry Manufacturing and Controls

This supplement did not contain new information relating to the chemistry, manufacturing and controls (CMC) for the production of eculizumab.

4.2 Clinical Microbiology

This supplement did not contain new clinical microbiology information.

4.3 Preclinical Pharmacology/Toxicology

This supplement did not contain new preclinical pharmacology/toxicology information.

4.4 Clinical Pharmacology

This efficacy supplement contained the following clinical pharmacology information pertaining to the use of eculizumab for the treatment of atypical hemolytic uremic syndrome (aHUS):

- Scientific rationale for how the binding of eculizumab to human complement protein C5 interferes with the pathophysiology of aHUS.
- Rationale for the proposed dosing regimens for the treatment of adult and pediatric patients with aHUS.
 - The applicant indicated that the dosing regimen was chosen based on pharmacokinetic (PK) modeling to maintain a target trough level of **≥ 50 µg/mL to maintain early, “complete,” and “sustained” terminal** complement inhibition, which deemed important in order to mitigate or avoid complications of thrombotic microangiopathy (TMA).
- Population pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation analyses from data collected in studies C08-002A/B, C08-003A/B, and C09-001r to derive exposure information (AUC, C_{max} , C_{min}) for eculizumab in aHUS patients and support the dosing strategy in various body weight groups.
- Results from assays for human anti-human antibody (HAHA) responses in aHUS patients.
 - One patient, who was diagnosed with systemic lupus erythematosus shortly after receiving a single dose of eculizumab, developed an anti-eculizumab antibody. There was no evidence of eculizumab neutralization or intolerance in this patient. However, because this patient was discharged from the study shortly after receipt of a single dose of eculizumab, the influence of development of anti-eculizumab antibodies in this patient on the PK of eculizumab could not be determined.

The clinical pharmacology team concluded that the clinical pharmacology data submitted with this application was sufficient to support the proposed dosing regimen. For more details, please refer to the clinical pharmacology review conducted by Bahru A. Habtemariam, PharmD (Primary Reviewer); Julie Bullock, PharmD (Secondary Reviewer); and Christine Garnett, PharmD (Pharmacometrics Secondary Reviewer).

4.4.1 Mechanism of Action

Eculizumab inhibits terminal complement mediated thrombotic microangiopathy (TMA) in patients with aHUS by binding to the complement protein C5, preventing cleavage of C5 to C5a and C5b, which in turn prevents the generation of the terminal complement complex C5b-9.

4.4.2 Pharmacodynamics

The sponsor performed exposure-response analyses for efficacy endpoints including TMA event-free status, change in renal function, and hematologic normalization. These analyses showed that the proportion of patients who achieved TMA event-free status, hematologic normalization, or a GFR improvement of at least 15 mL/min was not influenced by eculizumab exposure, body weight, or patient age. The clinical pharmacology reviewer concluded that this finding suggested that the selected doses provide sufficient exposure in patients of varying age and size.

Safety analyses indicated that there did not appear to be a relationship between eculizumab exposure and infectious or hypertensive adverse events in patients with aHUS.

Serial measurement of serum complement levels of patients enrolled in Studies C08-002 and Study C08-003 provided additional support for the proposed dosage regimens. Compared to baseline, a 50% and 62% reduction in median C5 activity was observed in studies C08-002 and C08-003, respectively. In addition, in most patients, CH50 levels were markedly reduced or undetectable after Day 7 of therapy.

4.4.3 Pharmacokinetics

Population pharmacokinetics (PK) analyses demonstrated that clearance and volume of distribution of eculizumab increased with body weight. The estimated clearance, volume of distribution, and half-life of eculizumab in a 70 kg patient were 0.014 L/hr, 5.6 L, and 12.4 days, respectively. The PK data derived from Studies C08-002 and C08-003 showed that the proposed weight cut-off based doses of eculizumab resulted in similar AUC values across the different weight groups. Age, race, gender, renal function, hepatic function, and the presence of auto-antibodies did not appear to affect eculizumab PK.

Plasma exchange caused a 50% decline in eculizumab concentrations following a 1 hour intervention, increased the rate of the clearance to 3.66 L/hr and reduced the half-life to 1.3 hours.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

Table 5 lists the clinical studies submitted in support of the sBLA. Data from these studies serve as the primary basis for the safety and efficacy evaluation.

Table 5: Clinical Studies Submitted by the Applicant in Support of sBLA 125166

Study Number	Population	Design	Endpoints	Number of Patients	Treatment Duration	Study Status/ Report Type
C08-002 A/B	Patients with aHUS resistant to plasma therapy	Single arm, open label	Efficacy, Safety, Pharmacokinetic	17	26 weeks and extension	Ongoing/ Full
C08-003 A/B	Patients with aHUS sensitive to plasma therapy	Single arm, open label	Efficacy, Safety, Pharmacokinetic	17	26 weeks and extension	Ongoing/ Full
C09-001r	Patients with aHUS	Non-interventional, retrospective	Safety, Efficacy	30	Varied	Complete; Full

5.2 Review Strategy

The review of this sBLA was conducted by a single reviewer. Studies C08-002A/B (hereafter referred to as "Study C08-002") and C08-003 (hereafter referred to as "Study C08-003") provided the primary basis for the review of safety and efficacy of the review of eculizumab for the treatment of adult patients with aHUS. Study C09-001r provided the primary basis for the review of the safety and efficacy of eculizumab for the treatment of pediatric patients with aHUS, and supportive data for the review of eculizumab for the treatment of adult patients.

The primary assessment of the efficacy and safety of eculizumab for the treatment of aHUS is derived from the original submission. Safety and efficacy data, including clinical study reports, case report forms, and datasets, were reviewed for Studies C08-002 A/B, C08-003 A/B, and C09-001r. In addition, the 120-day safety update, sponsor's responses to clinical inquiries during the review process, and Periodic Safety Update Report for the PNH indication were reviewed.

The principal review activities for this sBLA included:

- Review of the electronic submission of the sBLA
- Review of applicant responses to clinical queries
- Review of sponsor presentation slides to FDA on May 9, 2011
- Reproduction or auditing of key efficacy and safety analyses with JMP using raw datasets provided by the applicant
- Additional exploratory analyses of safety and efficacy data using the JMP tool
- Consultation with external experts (special government employees) with expertise in pediatric nephrology and pediatric hematology regarding key aspects of this application.

No new chemistry manufacturing and controls (CMC), clinical microbiology, or preclinical pharmacology/toxicology (PT) data were included in this sBLA submission.

5.3 Discussion of Individual Studies/Clinical Trials

Two prospective single arm studies (Study C08-002 A/B and Study C08-003 A/B) and one retrospective study (C09-001r) evaluated the safety and efficacy of eculizumab for the treatment of aHUS.

- Study C08-002 studied the effect of eculizumab therapy in patients with aHUS who displayed signs of thrombotic microangiopathy (TMA) despite receiving at least four plasma therapy (PT) treatments the week prior to screening. Sixteen adults and one adolescent patient enrolled in this trial.
- Study C08-003 studied eculizumab in patients with aHUS undergoing chronic plasma therapy (PT) 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. Fifteen adults and five adolescent patients enrolled in this trial.
- Study C09-001r was a retrospective study of patients who received eculizumab outside of an Alexion-sponsored trial for the treatment of aHUS between 2007 and December 2009. Nineteen children and eleven adults enrolled in this trial.

All three studies evaluated the effect of eculizumab therapy on several endpoints related to thrombotic microangiopathy (TMA). 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 intervention rate (defined as the number of plasma therapy interventions and new or increased frequency of dialyses required per patient per day).

5.3.1 Study C08-002 A/B (Patients with aHUS resistant to plasma therapy)

Study C08-002A/B was an open label, single arm, multicenter clinical trial of eculizumab in adults and adolescents with plasma-therapy resistant aHUS. Two separate protocols were followed during the conduct of this study: one for adult patients, and one for adolescent patients. The protocols differed primarily with respect to the age of the population studied. Study C08-002A required patients to be at least 18 years of age, and Study C08-003B enrolled patients between the ages of 12 and 18 who weighed at least 40 kg. Adolescent patients enrolled in C08-003B were treated using the same dosage regimen as adult patients. The goal sample size for the two studies combined was 15 patients.

Study C08-002A, entitled “An open-label, multi-center controlled clinical trial of eculizumab in adult patients with plasma therapy-resistant atypical hemolytic-uremic syndrome (aHUS),” enrolled adult patients.

Study C08-002B, entitled, “An open-label, multi-center controlled clinical trial of eculizumab in adolescent patients with plasma therapy-resistant atypical hemolytic-uremic syndrome (aHUS),” enrolled adolescent patients.

Fifteen sites enrolled a total of 17 patients, including a single adolescent patient, in five countries. Seven of the 17 enrolled patients (41%) were enrolled across six U.S. sites. The remaining patients were enrolled in France (6 patients in 5 sites), Germany (2 patients in 2 sites), Austria (1 patient), and the UK (1 patient). The first patient was enrolled on June 9, 2009, and the last patient enrolled on March 1, 2010. The study report for Study C08-002A/B contains data from the first patient visit until the date of primary data cut-off, September 8, 2010. The data cut-off date was chosen to allow a minimum duration of treatment of 26 weeks for all patients.

Table 6 shows the dates that the initial protocol and each amendment were finalized for Study C08-002 A/B. The following sections describe the final design of Study C08-002 A/B.

Table 6: Dates of Submission of Protocol and Protocol Amendments for Study C08-002

Protocol or Amendment	Submission Date	Notes
Global Protocol		
Version 1.0	05 November 2008	Original Protocol
Version 2.0	12 August 2009	
Version 3.0	26 August 2010	
Global Amendments:		
Amendment 1	08 September 2009	Incorporated the 3/25/09 and 5/08/09 country-specific Amendment 1 changes made in Germany and France into Global Protocol Version 2.0; provided justification for the dosing regimen; corrected the eculizumab dose prior to FFP intervention; updated entry criteria by adding washout periods instead of total exclusion; introduced antibiotic coverage for post-transplant patients on immunosuppressive treatment or aggressive plasma therapy; modified the protocol to be consistent with the summary of product characteristics for the marketing authorization application for Soliris; provided rationale for planned statistical analyses; introduced an optional extension period for patients who completed the 26 week course of therapy. Provision for acute ESA intervention was introduced, with patients allowed to be enrolled after a two week washout period prior to screening; required antibody coverage for patients likely to have an inadequate antibody response to the meningococcal vaccine;
Amendment 3	26 August 2010	Clarified ADAMTS-13 exclusion cut-off values to conform to original protocol definition, as well as include descriptions of intended statistical tests that were inadvertently omitted in Version 2.0;
Country Specific Protocol		
Version 1.1 (France only)	25 March 2009	
Version 1.1 (Germany only)	08 May 2009	
Version 2.1 (UK only)	17 November 2009	

Protocol or Amendment	Submission Date	Notes
Version 3.1 (UK only)	26 August 2010	
Country Specific Amendments		
Amendment 1 (France only)	25 March 2009	Added exclusion criteria for hypersensitivity to eculizumab; required adequate contraception methods during treatment and up to 5 months following discontinuation of study therapy for patients of childbearing potential; required study withdrawal of patients s/p renal transplant with newly developed antibody mediated resistance for whom rituximab is deemed the appropriate therapy.
Amendment 1 (Germany only)	08 May 2009	Restrict inclusion criteria for study C08-003B to restrict enrollment of patients between the ages of 12 up to 18 years to those weighing at least 40 kg.
Amendment 2 (France only)	12 November 2009	Minor changes made to summarize the changes and differences between the country specific (Version 1.1) and global protocol (Version 2.0)
Amendment 2 (Germany only)	08 September 2009	Minor changes made to summarize the changes and differences between the country specific (Version 1.1) and global protocol (Version 2.0)
Amendment 2 (UK only)	16 November 2009	Suggested that the extension treatment period last 2 years after the first 26-week treatment period.
Amendment 4 (UK only)	26 August 2010	Reestablish the ADAMTS-13 activity exclusion cut-off value to conform to the original protocol definition

Following the publication of aHUS guidelines in 2009 and discussions with FDA and the Committee of Human Medicinal Product (CHMP) regarding the development program for treatment of aHUS, a final statistical analysis plan amendment (SAP Amendment 1, dated October 28, 2010), incorporated the following changes:

- Addition of another primary endpoint, Hematologic Normalization (formerly called Complete Hematologic Response in background documents submitted to the FDA), defined as normalization of both platelet count and LDH sustained for a minimum of two consecutive measurements spanning an interval of at least four weeks.
- Addition of another secondary endpoint: Complete TMA Response, defined as Hematologic Normalization plus improvement in renal function defined as a 25% reduction from baseline in serum creatinine sustained for two consecutive measurements for at least four weeks.

- Frequency of plasma therapy, platelet count, LDH, eGFR, hemoglobin and creatinine levels were selected as endpoints to establish quantitative differences (or improvement) between the pre-eculizumab treatment period or historical control and the eculizumab treatment period.
- Adjustment in the definition of CKD staging to comply with UK National Institute for Health and Clinical Excellence guidelines.
- Adjustments were made to exploratory endpoints
- Changes to scoring of the summary index for EuroQoL 5D were made to use the Time Trade-Off value set for the united States instead of using the EuroQoL scoring.
- The analysis population for safety and efficacy analyses was changed from the per-protocol population to the intent-to-treat population.
- Original plans for separate analyses in the adult and adolescent populations were abandoned.
- All efficacy variables except for platelet count change from baseline, were analyzed during the eculizumab treatment period to the data cut-off date, instead of following completion of 26 weeks of treatment. Only platelet count change from baseline was analyzed following completion of 26 weeks for therapy.
- Analysis of efficacy variables analyzed according to presence or absence of complement regulatory factor mutations, rather than **according to the patient's** complement regulatory protein genetic abnormality.
- Inferential statistical analyses of safety endpoints body weight and vital signs (blood pressure, heart rate, and temperature), eliminated.
- Changes were made to the methodology for presenting data on TMA Event-free status and modifications were made to the ANOVA model for the change in platelet count from baseline.

5.3.1.1 Study C08-002 A/B Objectives

The primary objective of the study was to assess the ability of eculizumab to reduce TMA as measured by platelet count change from baseline during the 26-week treatment period in patients with aHUS resistant to plasma therapy. If the endpoint of platelet change from baseline was statistically significant, the analysis of the proportion of patients who achieved hematologic normalization from baseline through 26 weeks as well as to the data cut-off date was planned.

Secondary objectives were to measure the effect of eculizumab on the following parameters during the eculizumab treatment period and/or through the data cut-off date:

- TMA Intervention Rate (the number of plasma infusions and dialysis events/patient/day)
- TMA Event-Free status, defined as the absence of a 25% or greater decrease in platelet count compared to baseline, plasma therapy, and new dialysis for at least 12 weeks during eculizumab therapy
- Quality of Life measures
- Renal function

- Hemoglobin
- Complete TMA response (hematologic normalization plus improvement in renal function, defined as a 25% reduction from baseline in serum creatinine sustained for at least four weeks).

Other secondary objectives included the characterization of safety and tolerability of eculizumab in patients with aHUS; assessment of pharmacokinetic and pharmacodynamic properties of eculizumab; and quantification of differences in achievement of pre-defined levels of improvement in frequency of plasma therapy required, platelet counts, LDH, eGFR, hemoglobin, and creatinine.

5.3.1.2 Study C08-002 A/B Eligibility Criteria

Adult and adolescent patients were required to exhibit a decrease in platelet count despite at least four plasma therapy treatments in the week prior to screening. In addition, they were required to have presented with the typical signs of thrombotic thrombocytopenia, including decreased platelet count, microangiopathic hemolysis (increased LDH), and impaired renal function (increased creatinine). aHUS. The major inclusion and exclusion criteria for Study C08-002 A/B are listed below (adapted from protocol for brevity).

Inclusion Criteria

- ≥ 18 years (C08-002A) or between ages 12 and 18 years of age and weighing at least 40 kg. (C08-002B)
- Either newly diagnosed aHUS, relapsed aHUS, or post-transplant recurrence of aHUS
- Fulfillment of the following platelet count criteria:
 - Occurrence of a decrease in platelet count despite a minimum of 4 plasma therapy treatments in the week immediately prior to screening.
 - Screening platelet count $< 150,000/\mu\text{l}$
 - Screening platelet count at least 25% lower than the average of 3 platelet counts obtained during the most recent TMA remission, obtained at least one month apart during that remission prior to **screening ("the average remission platelet count"**
 - If historical counts unavailable, platelet count at the onset of the current aHUS exacerbation must be $\leq 75,000/\mu\text{l}$, and platelet count at screening must have been $\leq 100,000/\mu\text{l}$ at despite at least 5 plasma therapy infusions the week prior to screening.
- Known complement regulatory protein genetic abnormality:
 - Category 1: Factor H deficiency, Factor I deficiency, abnormal factor interaction (CFH/CFI FFP Group), or deletions of the CFHR1 and CFHR3 genes.
 - Category 2: Complement Protein 3, abnormal factor interaction (C3) or Factor B Gain of Function
 - Category 3: Anti-CFH Antibody (Anti-CFH Group)

- Category 4: MCP deficiency (MCP Group)
- Patients without documented complement mutation or known anti-CFH antibody eligible if other etiologies of HUS ruled out (as confirmed by the exclusion criteria); Patients meeting these conditions were assigned to Category 5.
- LDH $\geq$ ULN, unless patient receiving plasma exchange and LDH was $\geq$ ULN at the onset of aHUS exacerbation.
- Creatinine level $\geq$ ULN for age (unless on dialysis for acute renal failure)
- For women of childbearing potential, practicing effective contraceptive regimen during the entire study duration
- Informed consent/assent

Exclusion Criteria

- Thrombotic Thrombocytopenia Purpura (TTP): ADAMTS-13 activity $<$ 5% prior to initiation of plasma therapy or at the time of screening
- HUS due to presence of one or more of the following:
 - Shiga toxin
 - Known HIV infection
 - Drug exposure
 - Infection
 - Bone marrow transplantation
 - Vitamin B12 deficiency
- Requirement for chronic dialysis
- Sepsis or active, untreated infection that confounds diagnosis of aHUS or impedes aHUS management
- Pregnancy or lactation
- Known Systemic Lupus Erythematosus (SLE) or antiphospholipid antibody syndrome
- Prior eculizumab therapy or hypersensitivity to eculizumab, murine proteins, or one of the excipients
- Receipt of IVIG within 8 weeks or rituximab within 12 weeks of screening
- Receipt of immunosuppressive therapy such as steroids, mTOR inhibitors, tacrolimus, unless part of an established post-transplant regimen or required for treatment of confirmed anti-CFH antibody and dose unchanged for at least four weeks; or patient experienced aHUS relapse immediately after transplant.
- ESA therapy unless on stable dose for at least four weeks prior to screening or discontinued at least two weeks prior to screening.

5.3.1.3 Study C08-002 A/B Protocol-Specified Study Discontinuation Criteria

Criteria for Patient Discontinuation from Study Treatment or Assessments

- Withdrawal of consent
- Investigator decision

- aHUS exacerbation requiring IVIG or immunosuppressive therapies such as mTOR inhibitors, or tacrolimus, at the discretion of the investigator and sponsor
- For patients s/p kidney transplant, development of antibody-mediated rejection (C4d positive renal biopsy) requiring rituximab therapy
- Pregnancy
- Determination that patient did not fulfill eligibility criteria following initiation of eculizumab therapy

5.3.1.4 Study C08-002 A/B Prohibited or Restricted Concomitant Therapies

- IVIG and rituximab were prohibited during the study and within 8 weeks and 12 weeks prior to enrollment, respectively.
- Stable doses of immunosuppressive therapies were permitted only as part of an established post-transplant regimen or if required for treatment of confirmed anti-CFH antibody or aHUS relapse immediately after transplant.
- ESA therapy was allowed on study only if patients were maintained on a stable dose for at least four weeks prior to screening; patients who were previously treated with ESAs must have discontinued ESA therapy at least two weeks prior to screening.
- Use of plasma therapy within the first 96 hours had to be approved by the sponsor. After 96 hours, plasma therapy was to be administered using the same regimen employed prior to initiation of eculizumab therapy at the discretion of the investigator, to maintain the platelet count at levels above the baseline pre-PT set point. Plasma therapy was to administered only if patients demonstrated a compelling medical need, manifested as one or more of the following:
 - New decrease in platelet count to a level below 150,000/ μ l that is also 25% below the pre-plasma therapy baseline set-point value
 - New decrease in platelet count to a level below 40,000/ μ l
 - New neurological, renal or other clinical signs prospectively defined for each patient
- Dialysis was not permitted within the first 48-hour period following the first eculizumab dose, unless approved by the sponsor. Additionally, patients must have exhibited a compelling medical need, defined as:
 - Hypervolemia unresponsive to diuretics
 - Refractory electrolyte imbalance
 - New-onset uremic encephalopathy

5.3.1.5 Study C08-002 A/B Study Design and Treatment Plan

There were four stages in the study: the Screening Period, Treatment Period, Extension Period, and Post-Treatment Period. The eculizumab treatment period commenced with the first eculizumab dose and continued for 26 weeks. After 26 weeks, patients had the option of continuing eculizumab treatment during the extension period, which would last until the product became commercially available at their treatment site.

The treatment regimen included a four week induction phase followed by a maintenance phase. During induction, patients received 900 mg of eculizumab intravenously every week for four weeks. Starting on Week 5 (+/- 2 days), patients received maintenance therapy consisting of 1200 mg eculizumab every 14 days (+/- 2 days). PK modeling predicted that this dosing regimen would achieve minimum trough eculizumab levels of 35 µg/mL, resulting in complete inhibition of terminal complement activity in both males and females, after the first week of therapy. Patients received the first dose of eculizumab between one and six hours after the last Qualifying Plasma Therapy Episode.

The schedule of events for the treatment and extension portions of Study C08-002 listed are listed in Table 7 and Table 8, respectively (copied from submission).

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Table 7: Schedule of Events for Study C08-002 A/B (copied from submission)

Study Phase	Screen Phase	Treatment Phase														
		Induction Period							Maintenance Period							
		Screen	Month 1							Month 2		Month 3			Month 4	
Visit Number	1	2 ¹	3	4	5	6	7	8	9	10	11	12	13	14	15	
Days	-3-0	0	1	2	3	4	7	14	21	28	42	56	70	84	98	
Weeks		Wk 0					Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	
							+2D	+2D	+2D	+2D	+2D	+2D	+2D	+2D	+2D	
Informed Consent, Assent (if applicable)	X															
Medical History	X															
Historical Data Review ²	X															
EuroQol 5D	X	X				X	X	X	X	X	X		X	X	X	
Thromboembolic events (MAVE) ³	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination	X															
12-lead ECG	X															
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PI Record Update	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Health Economic Data		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events/Events related to aHUS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Genetic Mutation Test (if applicable)	X															

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Table 7 (cont) Schedule of Events for Study C08-002 A/B (copied from submission)

Study Phase	Screen Phase	Treatment Phase														
		Induction Period							Maintenance Period							
Study Month	Screen	Month 1							Month 2		Month 3			Month 4		
Visit Number	1	2 ¹	3	4	5	6	7	8	9	10	11	12	13	14	15	
Days	-3-0	0	1	2	3	4	7	14	21	28	42	56	70	84	98	
Screening and Baseline Paired Platelet Count Samples	X ¹⁶	X ^{15, 17}														
Clinical Lab (Hema, Chem. &UA) Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Pregnancy Test ⁴	X															
Hemolytic Markers ⁵	X	X ¹³	X	X	X	X	X	X	X	X	X	X			X	
Pro-thrombotic Measures ⁶	X	X ¹³	X	X	X	X	X	X	X	X	X	X			X	
Pro-inflammatory Markers ⁷	X	X ¹³	X	X	X	X	X	X	X	X	X	X			X	
Complement Markers ⁸	X	X ¹³	X	X	X	X	X	X	X	X	X	X			X	
Renal Function Measures ⁹	X	X ¹³	X	X	X	X	X	X	X	X	X	X			X	
ADAMTS-13 Inhibitor Assay	X															
Chronic Kidney Disease Stage Assessment	X	X								X		X			X	
Dialysis Assessment	X	X								X		X			X	
Vaccination: N.Meningitidis ¹⁰	X	X														
HAHA	X	X								X					X	
Confirmation of Inclusion and Exclusion Criteria	X	X														
PK/PD ¹¹		BL/P	X			X	T			T	T				T	
Dosing Visit; Dose (mg) ¹²		900					900	900	900	1200	1200	1200	1200		1200	1200

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Table 7 (cont) Schedule of Events for Study C08-002 A/B (copied from submission)

Study Phase	Treatment Phase						Post-Treat	
	Maintenance Period							
	Month 5		Month 6		Month 7			
Study Month	16	17	18	19	20	21/ET	Unscheduled Visits	Weeks 1-3 ¹⁸
Visit Number	112	126	140	154	168	182		
Days	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26		
Weeks	+2D	+2D	+2D	+2D	+2D	+2D		
EuroOol 5D		X		X		X		
Thromboembolic events (MAVE) ³	X	X	X	X	X	X	X ¹⁸	
Physical Examination		X				X		
12-lead ECG		X				X		
Vital Signs	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
PT Record Update	X	X	X	X	X	X	X	
Health Economic Data Review	X	X	X	X	X	X	X ¹⁹	
Adverse Events/Events related to aHUS	X	X	X	X	X	X	X	X
Genetic Mutation Test						X ²⁰		
Clinical Lab (Hema, Chem. &UA) Tests	X	X	X	X	X	X	X ¹⁴	X
Serum Pregnancy test ⁴						X		
Hemolytic Markers ⁵	X		X			X		
Pro-thrombotic Markers ⁶	X		X			X		
Pro-inflammatory Markers ⁷	X		X			X		

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Table 7 (cont) Schedule of Events for Study C08-002 A/B (copied from submission)

Study Phase	Treatment Phase						Post-Treat Phase	
	Maintenance Period							
Study Month	Month 5		Month 6		Month 7		Unscheduled Visits	Weeks 1-8 ¹⁵
Visit Number	16	17	18	19	20	21/ET		
Days	112	126	140	154	168	182		
Weeks	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26		
	*2D	*2D	*2D	*2D	*2D	*2D		
Complement Markers ⁷	X		X			X		
Renal Function Measures ⁸	X		X			X		
Chronic Kidney Disease Stage Assessment	X		X			X		
Dialysis Assessment	X		X			X		
HAHA						X		
PK/PD ¹¹						T		
Dosing Visit; Dose (mg) ¹²								

¹⁵ Visit 1 and Visit 2 may have been combined. If Visit 1 and Visit 2 were combined, the 2 averaged platelet counts collected more than 1 hour and less than 4 hours apart and drawn immediately prior to the Qualifying PT Episode acted as both inclusion criteria and Platelet Count Pre-PT Baseline Set-Point determination.

¹⁶ Historical data review was completed for each patient and recorded on the CRF. Review to include recording of all prior exacerbations of aHUS, platelet counts associated with each exacerbation and treatments or therapies administered in the 12 months prior to the screening visit. Additionally recorded information on implementation of dialysis, renal transplantation or nephrectomy procedures, as well as renal function measures and potential emergent neurological, renal or other sequelae for each historical exacerbation and prospectively identified by the PI for assessment during the Treatment Period.

¹⁷ Information on MAVE – large and small vessel thrombosis as well as microthrombosis, including date location and method of diagnosis

¹⁸ Pregnancy tests were performed on all women at Visits 1 and 21/ET. Pregnancy tests may also have been performed at any visit at the PI's discretion.

¹⁹ Hemolytic markers (Serum LDH, plasma haptoglobin, plasma free hemoglobin, reticulocytes, schistocytes/HPF and presence or absence of schistocytes)

²⁰ Prothrombotic markers (Plasma fibrinogen, serum fibrin split products, plasma D-dimer, prothrombin fragment 1.2, platelet P-selectin, thrombin-anti-thrombin (TAT) complexes, neutrophil-platelet aggregates and monocyte-platelet aggregates)

²¹ Pro-inflammatory Markers (serum IL-6, serum TNF-alpha, IL1-beta, IL2R, plasma tissue factor, CRP, ESR)

²² Complement Markers such as (C3, AP50, C3, C4, C4d, C5, and sC5b-9)

²³ Renal function measures (serum creatinine, urinary protein/creatinine ratio, eGFR).

²⁴ If all eligibility criteria were met, patients were vaccinated against N. meningitidis (if not already vaccinated within the time period of active coverage specified by the vaccine manufacturers). Patients must have been vaccinated at least 14 days prior to receiving the first eculizumab infusion, or have been

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Table 7 (cont) Schedule of Events for Study C08-002 A/B (copied from submission)

vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination. If consideration was given to postpone vaccination for patients who were status post (s/p) renal transplant and treated with immunosuppressive agents, the Investigator was to discuss in advance with the Sponsor, at what point vaccination was expected and how appropriate antibiotic coverage was to be managed until 14 days after the vaccination. Provided patient ID card prior to first dose of eculizumab.

- ¹¹ Baseline (BL) and trough (T) samples for PK and PD testing were to be taken 5-90 minutes before eculizumab infusion. Peak (P) samples for PK and PD testing were to be taken 60 minutes after the completion of eculizumab infusion. On Day 1, Trough draw was to be collected 24 hours post completion of eculizumab infusion. If the patient received PE, PPH or FFP infusion, PK/PD sampling was to occur [1] 5-90 minutes prior to PE, PPH, or FFP or infusion [2] 60 minutes after PE, PPH, or FFP infusion and 5-90 minutes before eculizumab infusion, and [3] at 60 minutes after the completion of eculizumab infusion.
- ¹² 600 mg of eculizumab was to be administered after PE, PPH, or before each FFP event per each 2 units.
- ¹³ Laboratory tests were performed at the central laboratory and were collected immediately prior to the Qualifying PT Episode.
- ¹⁴ Unscheduled visit for PT intervention was to include collection of platelet counts immediately prior to PT administration and 24 hours after PT administration. Also collected hemoglobin and hematocrit, WBC counts, BUN, LDH, haptoglobin, urinalysis and urine protein/creatinine ratio immediately prior to PT administration and 2+ hours after PT administration.
- ¹⁵ Post-Treatment Period assessments were to be performed at 1 week, 2 weeks, four weeks and 8 weeks after last dose of eculizumab.
- ¹⁶ Collect Visit 1 Screening platelet counts as specified under Section 11.4.1.1 of the final study protocol (Appendix 16.1.1).
- ¹⁷ Collect two platelet counts were to be drawn immediately prior to the Qualifying PT Episode (the second platelet count was to be collected more than 1 and less than 4 hours after the first platelet count draw). The two platelet counts collected immediately prior to the Qualifying Episode was to be averaged to signify the Platelet Count Pre-PT Baseline Set-Point.
- ¹⁸ Was to be completed on General Visits only (see section 11.4.4.1 of the final study protocol (Appendix 16.1.1) for details)
- ¹⁹ Was to be completed on PT visits only (see section 11.4.4.2 of the final study protocol (Appendix 16.1.1) for details)
- ²⁰ Anti-CFH antibody titer sample at ET visit for any patients who were positive at screening.

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Table 8: Schedule of Events for Extension Phase of Study C08-002 A/B

(copied from submission)

Extension Treatment Phase						
	Repeating					
	Q2W	Q4W	Q8W	Q26W	Investigator Discretion	Exit Study Visit
EuroQol 5D		X				X
Thromboembolic events (MAVE)	X					X
Physical Examination				X		X
12-lead ECG				X		X
Vital Signs	X					X
Concomitant Medications	X					X
PT Record Update	X					X
Health Economic Data Review	X					X
Adverse Events/Events related to aHUS	X					X
Anti-CFH antibody Test	Anti-CFH antibody titer (performed at any early termination or exit visit only if positive at screening)					X
Clinical Lab (Hema, Chem. &UA) Tests		X				X
Serum Pregnancy test					X	X
Hemolytic Markers			X			X
Pro-thrombotic Markers			X			X
Pro-inflammatory Markers			X			X
Complement Markers			X			X
Renal Function Measures			X			X
Chronic Kidney Disease Stage Assessment		X				X
Dialysis Assessment		X				X
HAHA				X		X
PK/PD				X		X
Dosing (mg)	1200					

5.3.1.6 Sample Size/Statistical Plan for Study C08-002

- All patients in the intent-to-treat ITT population were analyzed for the efficacy and safety endpoints. In addition, efficacy endpoints were analyzed according to the presence or absence of complement regulatory factor mutations.
- The ITT population was defined as all patients who received any amount of eculizumab, and were considered evaluable for safety and efficacy analyses.
- Descriptive statistics were analyzed for continuous variables
- Frequency counts and percentages were calculated for categorical variables

Analysis of Primary Endpoints

- Platelet count change from baseline to the first 26 weeks of treatment was assessed using a linear model (ANOVA). Time and baseline were used as the main effects, and the patient was the random effect. Platelet count changes were compared at each post-dose day of measurement (excluding days 1 to 4) through Week 26. Statistical significance of a positive or negative increase in the change from baseline was assessed at the 5% level at each time point.
- If the protocol-specified primary endpoint, Platelet count change from baseline, was statistically significant, then the additional primary endpoint of Hematologic Normalization from baseline to the end of the first 26 weeks of the treatment period as well as to the end of study involvement was to be performed.
- No statistical adjustment for multiple comparisons was made.
- All statistical tests were assessed at the two-sided 5% level.
- Missing data was imputed.

Analysis of Key Secondary Efficacy Endpoints

- Secondary efficacy endpoints were analyzed during the eculizumab treatment period to the end of the 26 week treatment period, and through the data cut-off date.
- Two sided signed rank test was used to compare the difference in the pre- and post-TMA intervention rates. Difference in the pre and post eculizumab dose TMA intervention rate was calculated for each patient using the following algorithm:
 - To derive the post-eculizumab dose TMA intervention rate, the sum of the number of plasma therapy and dialysis interventions occurring from the fifteen days after the first eculizumab dose to the earlier of the first 26 weeks of **treatment or the patient's end of study** involvement was calculated. Then, this sum was divided by the number of total patient days.
 - To derive the pre-eculizumab dose TMA intervention rate, the sum of the number of plasma therapy and dialysis interventions occurring from the later of 26 weeks prior to the first eculizumab dose and the start date of the patient's **current aHUS** episode to 14 days after the first eculizumab dose was calculated. Then, this sum was divided by the number of total patient days.

- The difference between the pre and post-eculizumab TMA intervention rate was then obtained
- The point estimate and 95% confidence intervals for the proportion of patients attaining a TMA-Event Free state through 26 weeks and before the end of study involvement was also calculated. TMA-Event Free Status required absence of the following three components for at least 12 weeks:
 - decrease in platelet count by greater than 25% from the baseline level
 - requirement for plasma therapy
 - requirement for new dialysis.
- The time to the start of the first TMA-event free state was calculated.
- Change in Quality of Life compared to baseline as measured by the EuroQol 5D was assessed using an ANOVA model.
- Changes in the following parameters were analyzed using frequency counts, **proportions, and exact 95% CI's**:
 - Parameters of renal function parameters of CKD stage, creatinine, and eGFR were analyzed
 - Hemoglobin levels
- The number of patients achieving a complete TMA response (defined as Hematologic Normalization plus improvement in renal function defined as a 25% reduction from baseline in serum creatinine sustained for two consecutive measurements for at least four weeks) were tabulated and analyzed.
- Safety was assessed by assessment of adverse events, laboratory measurements, physical examination, vital signs, electrocardiograms.
- Comparisons of frequency of plasma therapy, platelet counts, lactate dehydrogenase, estimated GFR, hemoglobin, creatinine, and chronic kidney disease grade without dialysis occurring during the pre-treatment period or historical control and the eculizumab-treatment period were performed. These two time periods were chosen to be approximately equal lengths of time. Two types of tests were used in these comparisons: Signed rank tests were performed to assess differences in magnitudes of change in certain parameters between the two periods, and **McNemar's tests were used to assess differences in frequencies of attaining pre-defined levels of improvement.**

5.3.2 Study C08-003 A/B (Patients with aHUS sensitive to plasma therapy)

Study C08-003A/B was an open label, single arm, multicenter clinical trial of eculizumab in adults and adolescents with plasma-therapy sensitive aHUS. Two separate protocols were followed during the conduct of this study: one for adult patients, and one for adolescent patients. The protocols differed primarily with respect to the age of the population studied. Study C08-003A required patients to be at least 18 years of age,

and Study C08-003B enrolled patients between the ages of 12 and 18 who weighed at least 40 kg. Patients enrolled in C08-003B were treated using the same dosage regimen as adult patients. The goal sample size for the two studies combined was 20 to 30 patients.

Study C08-003A, entitled “An open-label, multi-center controlled clinical trial of eculizumab in adult patients with plasma therapy-sensitive atypical hemolytic-uremic syndrome (aHUS),” enrolled adult patients.

Study C08-003B, entitled, “An open-label, multi-center controlled clinical trial of eculizumab in adolescent patients with plasma therapy-sensitive atypical hemolytic-uremic syndrome (aHUS),” enrolled adolescent patients.

Sixteen sites enrolled a total of 23 patients, including five adolescent patients, in eight countries. Two of the 23 enrolled patients (9%) were enrolled in US sites, but failed screening and did not receive eculizumab therapy. An additional patient, enrolled in the Netherlands, also failed screening and did not receive eculizumab therapy. The remaining patients were enrolled in France (9 patients in 6 sites), the UK (3 patients in 2 sites), the Netherlands (3 patients in a single site), Canada (2 patients in a single site), Germany (1 patient), Italy (1 patient), and Sweden (1 patient). The first patient was enrolled on July 24, 2009, and the last patient enrolled on February 25, 2010. The study report for Study C08-002A/B contains data from the first patient visit until the date of primary data cut-off, October 18, 2010. The data cut-off date was chosen to allow a minimum duration of treatment of 26 weeks for all patients.

Table 9 shows the dates that the initial protocol and each amendment were finalized. In general, the protocol amendments incorporated into Study C08-003 paralleled those that were instituted for Study C08-002. The following sections describe the final design of Study C08-003 A/B.

Table 9: Dates of Submission of Protocol and Protocol Amendments for Study C08-003

Protocol or Amendment	Submission Date	Notes
Global Protocol		
Version 1.0	05 November 2008	Original Protocol
Version 2.0	18 August 2009	
Version 3.0	01 September 2010	
Global Amendments:		
Amendment 1	08 September 2009	Incorporated the 3/25/09 and 5/08/09 country-specific Amendment 1 changes made in Germany and France into Global Protocol

Protocol or Amendment	Submission Date	Notes
		Version 2.0; provided justification for the dosing regimen; corrected the eculizumab dose prior to FFP intervention; updated entry criteria by adding washout periods instead of total exclusion; introduced antibiotic coverage for post-transplant patients on immunosuppressive treatment or aggressive plasma therapy; provided rationale for planned statistical analyses; introduced an optional extension period for patients who completed the 26 week course of therapy. Provision for acute ESA intervention was introduced, with patients allowed to be enrolled after a two week washout period prior to screening; required antibody coverage for patients likely to have an inadequate antibody response to the meningococcal vaccine;
Amendment 3	1 September 2010	Clarified ADAMTS-13 exclusion cut-off values to conform to original protocol definition, as well as include descriptions of intended statistical tests that were inadvertently omitted in Version 2.0; Amendment 3 provided stages of CKD, as defined by the National Kidney Foundation.
Country Specific Protocol		
Version 1.1 (France only)	25 March 2009	
Version 1.1 (Germany only)	08 May 2009	
Version 2.1 (UK only)	17 November 2009	
Version 3.1 (UK only)	01 September 2010	
Country Specific Amendments		
Amendment 1 (France only)	25 March 2009	Added exclusion criteria for hypersensitivity to eculizumab; required adequate contraception methods during treatment and up to 5 months following discontinuation of study therapy for patients of childbearing potential; required study withdrawal of patients s/p renal transplant with newly developed antibody mediated resistance for whom rituximab is deemed the appropriate

Protocol or Amendment	Submission Date	Notes
		therapy.
Amendment 1 (Germany only)	08 May 2009	Restrict inclusion criteria for study C08-002B to restrict enrollment of patients between the ages of 12 up to 18 years to those weighing at least 40 kg.
Amendment 2 (France only)	12 November 2009	Minor changes made to summarize the changes and differences between the country specific (Version 1.1) and global protocol (Version 2.0)
Amendment 2 (Germany only)	08 September 2009	Minor changes made to summarize the changes and differences between the country specific (Version 1.1) and global protocol (Version 2.0)
Amendment 2 (UK only)	16 November 2009	Suggested that the extension treatment period last 2 years after the first 26-week treatment period.
Amendment 4 (UK only)	1 September 2010	Reestablish the ADAMTS-13 activity exclusion cut-off value to conform to the original protocol definition

Following the publication of aHUS guidelines in 2009 and discussions with FDA and the Committee of Human Medicinal Product (CHMP) regarding the development program for treatment of aHUS, a final statistical analysis plan amendment incorporated the following changes into the final statistical analysis plan (dated 1 November 2010):

- Addition of another primary endpoint, Hematologic Normalization (formerly called Complete Hematologic Response in background documents submitted to the FDA), defined as normalization of both platelet count and LDH sustained for a minimum of two consecutive measurements spanning an interval of at least four weeks.
- Addition of another secondary endpoint: Complete TMA Response, defined as Hematologic Normalization plus improvement in renal function defined as a 25% reduction from baseline in serum creatinine sustained for two consecutive measurements for at least four weeks.
- Frequency of plasma therapy, platelet count, LDH, eGFR, hemoglobin and creatinine levels were selected as endpoints to establish quantitative differences (or improvement) between the pre-eculizumab treatment period or historical control and the eculizumab treatment period.
- Adjustment in the definition of CKD staging to comply with UK National Institute for Health and Clinical Excellence guidelines.
- Adjustments were made to exploratory endpoints
- Changes to scoring of the summary index for EuroQoL 5D were made to use the Time Trade-Off value set for the united States instead of using the EuroQoL scoring.
- The analysis population for safety and efficacy analyses was changed from the per-protocol population to the intent-to-treat population.

- Original plans for separate analyses in the adult and adolescent populations were abandoned.
- All efficacy variables except for platelet count change from baseline, were analyzed during the eculizumab treatment period to the data cut-off date, instead of following completion of 26 weeks of treatment. Only platelet count change from baseline was analyzed following completion of 26 weeks for therapy.
- Analysis of efficacy variables analyzed according to presence or absence of complement regulatory factor mutations, rather than **according to the patient's** complement regulatory protein genetic abnormality.
- Inferential statistical analyses of safety endpoints body weight and vital signs (blood pressure, heart rate, and temperature), eliminated.
- Changes were made to the methodology for presenting data on TMA Event-free status and modifications were made to the ANOVA model for the change in platelet count from baseline.

5.3.2.1 Study C08-003 Objectives

The primary objective of Study C08-003 was to assess the ability of eculizumab to achieve TMA event-free status during the 26-week treatment period in patients with aHUS sensitive to plasma therapy. TMA event-free status was defined as the absences of all of the following for a minimum of 12 weeks:

- Decrease in platelet count of > 25% from the baseline set-point prior to plasma therapy
- Plasma therapy while receiving eculizumab
- New dialysis requirement.

If the primary objective was met, then an additional objective was to evaluate the proportion of patients who achieved hematologic normalization from baseline through 26 weeks as well as to the data cut-off date.

Secondary objectives were to measure the effect of eculizumab on the following parameters during the eculizumab treatment period and/or through the data cut-off date:

- TMA Intervention Rate (the number of plasma infusions and dialysis events/patient/day) compared to the TMA Intervention Rate during the observation period prior to the first eculizumab dose
- Platelet count change from baseline during the first 26 weeks of the treatment period.
- Quality of Life measures
- Renal function
- Hemoglobin
- Complete TMA response (hematologic normalization plus improvement in renal function, defined as a 25% reduction from baseline in serum creatinine sustained for at least four weeks).

Other secondary objectives included the characterization of safety and tolerability of eculizumab in patients with aHUS; assessment of pharmacokinetic and pharmacodynamic properties of eculizumab; and quantification of differences in achievement of pre-defined levels of improvement in frequency of plasma therapy required, platelet counts, LDH, eGFR, hemoglobin, and creatinine.

5.3.2.2 Study C08-003 Eligibility Criteria

Adult and adolescent patients were required to have received a minimum of one plasma therapy session every two weeks but no more than three plasma therapy sessions per week at an unchanged frequency for a minimum of eight weeks prior to the first dose of eculizumab. In addition, platelet counts were to remain stable during this period. The major inclusion and exclusion criteria for Study C08-003 A/B are listed below (adapted from protocol for brevity).

Inclusion Criteria

- ≥ 18 years (C08-003A) or between ages 12 and 18 years of age and weighing at least 40 kg. (C08-003B)
- Prior to the first dose of eculizumab, receipt of a minimum of one plasma therapy session every two weeks but no more than three plasma therapy sessions per week at an unchanged frequency for a minimum of eight weeks for the treatment of aHUS
- Platelet count Pre-PT Baseline Set-Point (average of two platelet counts collected at the end of the observation period) was within 75% of the average of the Pre-PT platelet counts collected at screening and during the observation period.
- Known complement regulatory protein genetic abnormality:
 - Category 1: Factor H deficiency, Factor I deficiency, abnormal factor interaction (CFH/CFI FFP Group), or deletions of the CFHR1 and CFHR3 genes.
 - Category 2: Complement Protein 3, abnormal factor interaction (C3) or Factor B Gain of Function
 - Category 3: Anti-CFH Antibody (Anti-CFH Group)
 - Category 4: MCP deficiency (MCP Group)
- Patients without documented complement mutation or known anti-CFH antibody eligible if other etiologies of HUS ruled out (as confirmed by the exclusion criteria); Patients meeting these conditions were assigned to Category 5.
- LDH $\geq$ ULN at screening or at the onset of the current aHUS exacerbation or other markers indicative of ongoing hemolysis (e.g. decreased haptoglobin, schistocytes) present.
- Creatinine level $\geq$ ULN for age
- For women of childbearing potential, practicing effective contraceptive regimen during the entire study duration
- Informed consent/assent

Exclusion Criteria

- Thrombotic Thrombocytopenia Purpura (TTP): ADAMTS-13 activity < 5% prior to initiation of plasma therapy or at the time of screening
- HUS due to presence of one or more of the following:
 - Shiga toxin
 - Known HIV infection
 - Drug exposure
 - Infection
 - Bone marrow transplantation
 - Vitamin B12 deficiency
- Sepsis or active, untreated infection that confounds diagnosis of aHUS or impedes aHUS management
- Pregnancy or lactation
- Known Systemic Lupus Erythematosus (SLE) or antiphospholipid antibody syndrome
- Prior eculizumab therapy or hypersensitivity to eculizumab, murine proteins, or one of the excipients
- Receipt of IVIG within 8 weeks or rituximab within 12 weeks of screening
- Receipt of immunosuppressive therapy such as steroids, mTOR inhibitors, tacrolimus, unless part of an established post-transplant regimen or required for treatment of confirmed anti-CFH antibody and dose unchanged for at least four weeks; or patient experienced aHUS relapse immediately after transplant.
- ESA therapy unless on stable dose for at least four weeks prior to screening or discontinued at least two weeks prior to screening.
- Malignancy within 5 years of screening

Reviewer note: Unlike Study C08-002, patients with a chronic dialysis requirement were eligible for enrollment in Study C08-003.

5.3.2.3 Study C08-003 Protocol-Specified Study Discontinuation Criteria

Reviewer note: the discontinuation criteria were similar in Studies C08-002 and C08-003.

Criteria for Patient Discontinuation from Study Treatment or Assessments

- Withdrawal of consent
- Investigator decision
- aHUS exacerbation requiring IVIG or immunosuppressive therapies such as mTOR inhibitors, or tacrolimus, at the discretion of the investigator and sponsor
- For patients s/p kidney transplant, development of antibody-mediated rejection (C4d positive renal biopsy) requiring rituximab therapy
- Pregnancy
- Determination that patient did not fulfill eligibility criteria following initiation of eculizumab therapy

5.3.2.4 Study C08-003 Prohibited or Restricted Concomitant Therapies

Reviewer note: the prohibited and restricted concomitant therapies were similar in Studies C08-002 and C08-003.

- IVIG and rituximab were prohibited during the study and within 8 weeks and 12 weeks prior to enrollment, respectively.
- Stable doses of immunosuppressive therapies were permitted only as part of an established post-transplant regimen or if required for treatment of confirmed anti-CFH antibody or aHUS relapse immediately after transplant.
- ESA therapy was allowed on study only if patients were maintained on a stable dose for at least four weeks prior to screening; patients who were previously treated with ESAs must have discontinued ESA therapy at least two weeks prior to screening.
- After entry into the trial, patients were not permitted to receive PT during the following time intervals, based upon previous PT requirements, unless there was compelling medical need:
 - For patients previously requiring PT once weekly, no PT within the first 2 weeks following the first eculizumab dose
 - For patients previously requiring PT twice weekly, no PT within the week following the first eculizumab dose
 - For patients previously requiring PT three times per week, no PT within 96 hours following the first eculizumab dose
- During the treatment period, plasma therapy was to be administered using the same regimen employed prior to initiation of eculizumab therapy at the discretion of the investigator. Plasma therapy was to administered only if patients demonstrated a compelling medical need, manifested as one or more of the following:
 - New decrease in platelet count to a level below 150,000/ μ l that is also 25% below the pre-plasma therapy baseline set-point value
 - New decrease in platelet count to a level below 40,000/ μ l
 - New neurological, renal or other clinical signs prospectively defined for each patient.
- Unless patients required chronic dialysis prior to entry into the study, dialysis was not permitted within the first 48-hour period following the first eculizumab dose, unless approved by the sponsor.

5.3.2.5 Study C08-003 Study Design and Treatment Plan

There were four stages in the study: the Screening Period, Treatment Period, Extension Period, and Post-Treatment Period. The eculizumab treatment period commenced with the first eculizumab dose and continued for 26 weeks. After 26

weeks, patients had the option of continuing eculizumab treatment during the extension period, which would last until the product became commercially available at their treatment site.

The treatment regimen included a four week induction phase followed by a maintenance phase. During induction, adult and adolescent patients received 900 mg of eculizumab intravenously every week for four weeks. Starting on Week 5 (+/- 2 days), patients received maintenance therapy consisting of 1200 mg eculizumab every 14 days (+/- 2 days). PK modeling predicted that this dosing regimen would achieve minimum trough eculizumab levels of 35 µg/mL, resulting in complete inhibition of terminal complement activity in both males and females, after the first week of therapy. Patients received the first dose of eculizumab between one and six hours after the last Qualifying Plasma Therapy Episode.

The schedule of events for the treatment and extension portions of Study C08-003 are listed in Table 10 and Table 11, respectively (copied from submission).

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Table 10: Schedule of Events for Study C08-003 A/B (copied from submission)

Study Phase	Screen Phase		Treatment Phase											
	Screen	OBS Period	Induction Period								Maintenance Period			
Study Month	-2.5 to 0	-2.0 to 0	Month 1								Month 2		Month 3	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Days	-14 to 0	OBS Day 0	Txt Day 0	1	2	3	4	7	14	21	28	42	56	70
Weeks	-10 to -8 Weeks	-8 Weeks	Wk 0	.	.	.	.	Wk 1 ±2D	Wk 2 ±2D	Wk 3 ±2D	Wk 4 ±2D	Wk 6 ±2D	Wk 8 ±2D	Wk 10 ±2D
Informed Consent	X	.	.	.	.	.	.	.	.	.	.	.	.	.
Medical History	X	.	.	.	.	.	.	.	.	.	.	.	.	.
Historical Data Review ¹	X	.	.	.	.	.	.	.	.	.	.	.	.	.
EuroQol 5D	X	.	X	.	.	.	.	X	X	X	X	X	X	X
Thromboembolic events (MAVE) ²	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	.	.	.	.	.	.	.	.	.	.	.	.	.
12-lead ECG	X	.	.	.	.	.	.	.	.	.	.	.	.	.
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT Record Update	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Economic Data Review	.	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events/Events related to aHUS	.	X	X	X	X	X	X	X	X	X	X	X	X	X
Genetic Mutation Test (if applicable)	X	.	.	.	.	.	.	.	.	.	.	.	.	.

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Table 10 (cont) Schedule of Events for Study C08-003 A/B (copied from submission)

Study Phase	Screen Phase		Treatment Phase											
	Screen	OBS Period	Induction Period								Maintenance Period			
Study Month	-2.5 to 0	-2.0 to 0	Month 1								Month 2		Month 3	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Days	-14 to 0	OBS Day 0	Txt Day 0	1	2	3	4	7	14	21	28	42	56	70
Weeks	-10 to -8 Weeks	-8 Weeks	Wk 0	.	.	.	.	Wk 1 ±2D	Wk 2 ±2D	Wk 3 ±2D	Wk 4 ±2D	Wk 6 ±2D	Wk 8 ±2D	Wk 10 ±2D
Screening and Baseline Paired Platelet Count Samples	X ¹⁴	X ¹⁷	.	.	.	.	.	.	.	.	.	.	.	.
Clinical Lab Tests (Hema, Chem. & UA)	X ¹⁵	X	X ¹²	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy test ⁵	X	.	X	.	.	.	.	.	.	.	.	.	.	.
Pro Thrombotic Measures ²	X	X	X ¹²	X	X	X	X	X	X	X	X	.	X	.
Pro Inflammatory Markers ⁶	X	X	X ¹²	X	X	X	X	X	X	X	X	.	X	.
Complement Markers ⁷	X	X	X ¹²	X	X	X	X	X	X	X	X	.	X	.
Renal Function Measures ³	X	X	X ¹²	X	X	X	X	X	X	X	X	.	X	.
ADAMTS-13 Inhibitor Assay	X	.	.	.	.	.	.	.	.	.	.	.	.	.
Chronic Kidney Disease Stage Assessment	X	.	X	.	.	.	.	.	.	.	X	.	X	.

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Table 10 (cont) Schedule of Events for Study C08-003 A/B (copied from submission)

Study Phase	Screen Phase		Treatment Phase											
	Screen	OBS Period	Induction Period								Maintenance Period			
Study Month	-2.5 to 0	-2.0 to 0	Month 1								Month 2	Month 3		
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Days	-14 to 0	OBS Day 0	Txt Day 0	1	2	3	4	7	14	21	28	42	56	70
Dialysis Assessment	X	.	X	.	.	.	.	.	.	.	X	.	X	.
Vaccination: <i>N. Meningitidis</i> ⁹	X	.	.	.	.	.	.	.	.	.	.	.	.	.
HAHA	.	.	X	.	.	.	.	.	.	.	X	.	.	.
Confirmation of Inclusion and Exclusion Criteria	X	X	.	.	.	.	.	.	.	.	.	.	.	.
PK/PD ¹⁰	.	.	BLP	X	.	.	X	T	.	.	T	T	.	.
Dosing Visit; Dose (mg) ¹¹	.	.	900	.	.	.	.	900	900	900	1200	1200	1200	1200

Study Phase	Treatment Phase								Post-Treat Phase	
	Maintenance Period									
Study Month	Month 4		Month 5		Month 6		Month 7		Unscheduled Visits	Weeks 1-3 ¹⁴
Visit Number	15	16	17	18	19	20	21	22/ET		
Days	84	98	112	126	140	154	168	182		
Week	Wk 12 ±2D	Wk 14 ±2D	Wk 16 ±2D	Wk 18 ±2D	Wk 20 ±2D	Wk 22 ±2D	Wk 24 ±2D	Wk 26 ±2D		
EuroQol 5D	X	X	.	X	.	X	.	X	.	.
Thromboembolic events (MAVE) ²	X	X	X	X	X	X	X	X	X ¹⁴	.
Physical Examination	.	.	.	X	.	.	.	X	.	.

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Table 10 (cont) Schedule of Events for Study C08-003 A/B (copied from submission)

Study Phase	Treatment Phase								Post-Treat Phase	
	Maintenance Period									
Study Month	Month 4		Month 5		Month 6		Month 7		Unscheduled Visits	Weeks 1-14
Visit Number	15	16	17	18	19	20	21	22/ET		
Days	84	98	112	126	140	154	168	182		
Week	Wk 12 ±2D	Wk 14 ±2D	Wk 16 ±2D	Wk 18 ±2D	Wk 20 ±2D	Wk 22 ±2D	Wk 24 ±2D	Wk 26 ±2D		
12-lead ECG	.	.	.	X	.	.	.	X	.	.
Vital Signs	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
PT Record Update	X	X	X	X	X	X	X	X	X	.
Health Economic Data Review	X	X	X	X	X	X	X	X	X ¹⁰	.
Adverse Events/Events related to sHUS	X	X	X	X	X	X	X	X	X	X
Genetic Mutation Test (if applicable)	.	.	.	.	.	.	.	X ¹⁰	.	.
Clinical Lab Tests (Hema, Chem. & UA)	X	X	X	X	X	X	X	X	X ¹¹	X
Serum Pregnancy test ⁸	.	.	.	.	.	.	.	X	.	.
Hemolytic Markers ⁴	X	.	X	.	X	.	.	X	.	.
Pro Thrombotic Measures ⁵	X	.	X	.	X	.	.	X	.	.
Pro Inflammatory Markers ⁶	X	.	X	.	X	.	.	X	.	.

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Table 10 (cont) Schedule of Events for Study C08-003 A/B (copied from submission)

Study Phase	Treatment Phase								Post-Treat Phase	
	Maintenance Period									
	Month 4		Month 5		Month 6		Month 7			
Study Month	Month 4		Month 5		Month 6		Month 7		Unscheduled Visits	Weeks 1-9 ¹⁴
Visit Number	15	16	17	18	19	20	21	22/ET		
Days	84	98	112	126	140	154	168	182		
Week	Wk 12 ±2D	Wk 14 ±2D	Wk 16 ±2D	Wk 18 ±2D	Wk 20 ±2D	Wk 22 ±2D	Wk 24 ±2D	Wk 26 ±2D		
Complement Markers ⁷	X	.	X	.	X	.	.	X	.	.
Renal Function Measures ⁸	X	.	X	.	X	.	.	X	.	.
Chronic Kidney Disease Stage Assessment	X	.	X	.	X	.	.	X	.	.
Dialysis Assessment	X	.	X	.	X	.	.	X	.	.
HAHA	X	.	.	.	.	.	.	X	.	.
PK/PD ¹⁸	T	.	.	.	.	.	.	T	.	.
Dosing Visit; Dose (mg) ¹¹	1200	1200	1200	1200	1200	1200	1200	1200	.	.

⁷Historical review was completed for each patient and recorded on the CRF. The review included recording all prior exacerbations of aHUS, platelet counts associated with each exacerbation, and treatments or therapies administered in the 12 months prior to the screening visit. Additionally, recorded information on implementation of dialysis, renal transplantation, or nephrectomy procedures, as well as renal function measures and potential emergent neurological, renal, or other sequelae for each historical exacerbation and prospectively identified by the PI for assessment during the Treatment Period.

⁸Information on MAVe – large and small vessel thrombosis as well as microthrombosis, including date, location, and method of diagnosis

⁹Pregnancy tests were performed on all women at Visits 1, 3 (prior to eculizumab dosing) and 22/ET. Pregnancy tests may have also been performed at any visit at the PI's discretion.

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Table 10 (cont) Schedule of Events for Study C08-003 A/B (copied from submission)

- ⁴ Hemolytic markers (Serum LDH, plasma haptoglobin, plasma free hemoglobin, reticulocytes, #schistocytes/HpF and presence or absence of schistocytes)
- ⁵ Prothrombotic markers (Plasma fibrinogen, serum fibrin split products, plasma D-dimer, prothrombin fragment 1.2, platelet P-selectin, thrombin-anti-thrombin (TAT) complexes, neutrophil-platelet aggregates, and monocyte-platelet aggregates)
- ⁶ Pro-inflammatory Markers (serum IL-6, serum TNF-alpha, IL1-beta, IL2R, plasma tissue factor, CRP, ESR)
- ⁷ Complement Markers such as (CH50, AP50, C3, C4, C4d, C5, and sC5b-C9)
- ⁸ Renal function measures (serum creatinine, urinary protein/gram creatinine, sGFR)
- ⁹ If all eligibility criteria are met, patients were vaccinated against *N. meningitidis* (if not already vaccinated within the time period of active coverage specified by the vaccine manufacturer). Note: Patients must have been vaccinated at least 14 days prior to receiving the first eculizumab infusion, or been vaccinated and received treatment with appropriate antibiotics until 14 days after the vaccination. Patients may have been vaccinated at Visit 1 or during the Observation Period as per the discretion of the PI. If consideration was given to postpone vaccination for patients who were s/p renal transplant, and treated with immunosuppressive agents, the Investigator must have discussed in advance with the Sponsor, at what point vaccination was expected and how appropriate antibiotic coverage was managed until 14 days after the vaccination.
- ¹⁰ Baseline (BL) and trough (T) samples for PK and PD testing were taken 5 – 90 minutes before eculizumab IV infusion. Peak samples for PK and PD testing were taken 60 minutes after the completion of eculizumab infusion. On Day 1, trough draw was collected 24 hours post-completion of eculizumab infusion. If the patient received PPH, PE, or FFP infusion, PK/PD sampling should have occurred [1] 5-90 minutes prior to PPH, PE, or FFP or infusion [2] 60 minutes after PPH, PE, or FFP infusion and 5-90 minutes before eculizumab infusion, and [3] at 60 minutes after the completion of eculizumab infusion.
- ¹¹ 600 mg of eculizumab was administered after every PPH, PE, or before each FFP event per each 2 Units.
- ¹² Laboratory tests were performed at the central laboratory and collected before the Qualifying PT Episode.
- ¹³ Unscheduled visit for PT intervention included collection of platelet counts before the PT administration and 24 hours after PT administration. Also collected hemoglobin and hematocrit, WBC counts, BUN, LDH, haptoglobin, urinalysis, and urine protein/creatinine ratio before PT administration and 24 hours after PT administration.
- ¹⁴ Post Treatment Period assessments were performed at 1 week, 2 weeks, 4 weeks and 8 weeks after the last dose of eculizumab.
- ¹⁵ Collected 2 platelet count samples - the second sample was collected more than 1 and less than 4 hours after the first platelet count is drawn. These two platelet counts were averaged to determine the screening platelet count.
- ¹⁶ Collected two platelet counts to be drawn at the end of the Observation Period and before the Qualifying PT Episode (the second platelet count to be collected more than 1 and less than 4 hours after the first platelet count draw). These two platelet counts were averaged to signify the Platelet Count Pre-PT Baseline Set-Point. The Platelet Count Pre-PT Baseline Set-Point (collected before the Qualifying PT Episode) must have been within 75% of the average of the pre-PT platelet counts collected at Screening and during the Observation Period. One set of platelet counts were sent to the site local lab for inclusion determination and the other set of platelet counts were sent to the central laboratory.
- ¹⁷ Procedures were collected on a weekly basis during the 8 week Observation Period
- ¹⁸ Completed on General Visits only (see section 11.4.5.1 of the protocol in Appendix 16.1.1 for details).
- ¹⁹ Completed on PT visits only (see section 11.4.5.2 of the protocol in Appendix 16.1.1 for details)
- ²⁰ Anti-CFH antibody titer sample at early termination visit for any patients who were positive at screening.
- ²¹ * = not applicable.

Table 11: Schedule of Events for Extension Phase of Study C08-003 A/B (copied from submission)

Extension Treatment Phase						
	Repeating				Investigator Discretion	Exit Study Visit
	Q2W	Q4W	Q6W	Q26W		
EuroQol 5D	.	X	.	.	.	X
Thromboembolic events (MAVE)	X	.	.	.	.	X
Physical Examination	.	.	.	X	.	X
12-lead ECG	.	.	.	X	.	X
Vital Signs	X	.	.	.	.	X
Concomitant Medications	X	.	.	.	.	X
PT Record Update	X	.	.	.	.	X
Health Economic Data Review	X	.	.	.	.	X
Adverse Events/Events related to aHUS	X	.	.	.	.	X
Anti-CFH antibody Test	Anti-CFH antibody titer (performed at any early termination or exit visit only if positive at screening)					X
Clinical Lab (Hema, Chem. &UA) Tests	.	X	.	.	.	X
Serum Pregnancy test	.	.	.	.	X	X
Hemolytic Markers	.	.	X	.	.	X
Pro-thrombotic Markers	.	.	X	.	.	X
Pro-inflammatory Markers	.	.	X	.	.	X
Complement Markers	.	.	X	.	.	X
Renal Function Measures	.	.	X	.	.	X
Chronic Kidney Disease Stage Assessment	.	X	.	.	.	X
Dialysis Assessment	.	X	.	.	.	X
HAHA	.	.	.	X	.	X
PK/PD	.	.	.	X	.	X
Dosing (mg)	1200	.	.	.	.	.

“.” = not applicable.

5.3.2.6 Sample Size/Statistical Plan for Study C08-003

- All patients in the intent-to-treat ITT population were analyzed for the efficacy and safety endpoints. In addition, efficacy endpoints were analyzed according to the presence or absence of complement regulatory factor mutations.
- The ITT population was defined as all patients who received any amount of eculizumab, and were considered evaluable for safety and efficacy analyses.
- Descriptive statistics were analyzed for continuous variables

- Frequency counts and percentages were calculated for categorical variables

Analysis of Primary Endpoints

- The proportion of patients who were TMA event-free prior to eculizumab treatment was compared to the proportion of patients who were TMA-event free during the 26 week treatment period with eculizumab using **McNemar's test**.
- TMA-Event Free Status required absence of the following three components for at least 12 weeks:
 - decrease in platelet count by greater than 25% from the baseline level
 - requirement for plasma therapy
 - requirement for new dialysis.
- **If McNemar's test of the protocol-specified** primary endpoint of TMA-event-free status from baseline to 26 weeks was statistically significant, then the additional primary endpoint of Hematologic Normalization from baseline to the end of the first 26 weeks of the treatment period as well as to the end of study involvement was to be performed.
- No statistical adjustment for multiple comparisons was made.
- All statistical tests were assessed at the two-sided 5% level.
- Missing data was imputed.

Analysis of Key Secondary Efficacy Endpoints

- Secondary efficacy endpoints were analyzed during the eculizumab treatment period to the end of the 26 week treatment period, and through the data cut-off date.
- Two sided signed rank test was used to compare the difference in the pre- and post-TMA intervention rates. Difference in the pre and post eculizumab dose TMA intervention rate was calculated for each patient using the following algorithm:
 - To derive the post-eculizumab dose TMA intervention rate, the sum of the number of plasma therapy and dialysis interventions occurring from the fifteen days after the first eculizumab dose to the earlier of the first 26 weeks of **treatment or the patient's end of study** involvement was calculated. Then, this sum was divided by the number of total patient days.
 - To derive the pre-eculizumab dose TMA intervention rate, the sum of the number of plasma therapy and dialysis interventions occurring from the later of 26 weeks prior to the first eculizumab dose and the start date of the patient's **current aHUS** episode to 14 days after the first eculizumab dose was calculated. Then, this sum was divided by the number of total patient days.
 - The difference between the pre and post-eculizumab TMA intervention rate was then obtained.
 - The two-sided rank test was used to calculate the p-value for comparison of the TMA intervention rates.

- Platelet count change from baseline to the first 26 weeks of treatment was assessed using an ANOVA model.
- Change in Quality of Life compared to baseline as measured by the EuroQol 5D was assessed using an ANOVA model.
- Changes in the following parameters were analyzed using frequency counts, **proportions, and exact 95% CI's**:
 - Parameters of renal function parameters of CKD stage, creatinine, and eGFR were analyzed
 - Hemoglobin levels
- The number of patients achieving a complete TMA response (defined as Hematologic Normalization plus improvement in renal function defined as a 25% reduction from baseline in serum creatinine sustained for two consecutive measurements for at least four weeks) were tabulated and analyzed.
- Safety was evaluated by assessment of adverse events, laboratory measurements, physical examination, vital signs, electrocardiograms.
- Comparisons of frequency of plasma therapy, platelet counts, lactate dehydrogenase, estimated GFR, hemoglobin, creatinine, and chronic kidney disease grade without dialysis occurring during the pre-treatment period or historical control and the eculizumab-treatment period were performed. These two time periods were chosen to be approximately equal lengths of time. Two types of tests were used in these comparisons: Signed rank tests were performed to assess differences in magnitudes of change in certain parameters between the two periods, and **McNemar's tests were used to assess differences in frequencies of attaining pre-defined levels of improvement.**

5.3.3 Study C09-001r (retrospective study of patients with aHUS)

Study C09-001r was a retrospective study evaluating the safety and effectiveness of eculizumab in patients with aHUS who received eculizumab outside of an Alexion-sponsored trial between 2007 and December 2009.

Except for a protocol amendment that affected only Spain, there were no protocol amendments to this study. In addition, several, mostly minor, changes to the analysis plan were instituted prior to the study database lock. These changes include the following:

- Adverse events of special interest/adverse drug reactions causally related to eculizumab were combined with adverse events to provide a consolidated listing of adverse events was made for each patient.
- The definition of pre-treatment dialysis events was changed from eight weeks prior to the first eculizumab dose to the period of 1 month prior to the first dose of

eculizumab. Dialysis events occurring during the first 14 days of eculizumab treatment were not considered post-dose dialysis events.

- Additional analyses were added based on FDA and CHMP recommendations to assess improvement in both hematologic parameters and renal function.

5.3.3.1 Study C09-001r Objectives

The objectives of this retrospective trial were to assess the safety and effectiveness of eculizumab in patients with aHUS who received eculizumab from 2007 through 2009 outside of an Alexion-sponsored trial.

5.3.3.2 Study C09-001r Eligibility Criteria

Study C09-001r was a retrospective trial of patients diagnosed with aHUS who received at least one dose of eculizumab between 2007 and December 2009, outside of an Alexion-sponsored clinical trial.

In response to an inquiry from the clinical team requesting a detailed explanation of how subjects and investigator sites were identified for inclusion in Study C09-001r, Alexion provided the following information:

Soliris identified 36 patients meeting these criteria who had received eculizumab either through compassionate drug distribution mechanisms (13 patients) or off-label use through commercial distribution channels (23 patients). Due to the Risk Management plan in place for Soliris, physicians or hospital pharmacists were required to register prior to obtaining Soliris. During the registration process, physicians indicate the diagnosis of the patient receiving eculizumab. Alexion stated that they usually discussed specific treatment options with physicians who requested Soliris for the treatment of a patient with aHUS. Alexion provided suggestions regarding drug administration and dosage regimen, particularly when a pediatric patient was treated. The Alexion Customer Operations group also maintained documentation of physician requests for Soliris for treatment of a patient with aHUS during the study period.

After the list of patients who received eculizumab for the treatment of aHUS during the study period was compiled, physicians of all 36 patients were contacted to solicit participation in the study. Thirty patients agreed to participate. The remaining patients were not included in the trial either because the patient or physician declined to participate in the study. A total of 30 adult and pediatric patients and were enrolled in 29 sites. Thirteen patients were enrolled in the U.S., and the remainder were enrolled in

Spain (5 patients), France (4 patients), Germany (2 patients), Austria (2 patients), the Netherlands (1 patient), Switzerland (2 patients), and Canada (1 patient).

5.3.3.3 Study Design and Treatment Plan

After informed consent was obtained, chart reviews were performed and data was transcribed into case report forms. The data collection was categorized into four periods:

- Initial Pre-Treatment Period: time from aHUS diagnosis up to 30 days prior to the first dose of eculizumab.
- 30-Day-Pre-Treatment Period
- Treatment Period: time from the start of eculizumab to its cessation or up to the time the patient signed the informed consent document if treatment was ongoing
- Post-Treatment Period: time from the end of the Treatment Period to signing the informed consent document.

During the initial Pre-Treatment period, the following information was collected:

- demographic information
- brief medical and surgical history, including the date of aHUS diagnosis, and the number of recurrent aHUS episodes
- family History related to aHUS
- history of major vascular events
- types of prior therapies for aHUS
- available laboratory parameters, including platelet count and serum creatinine levels at the time of initial aHUS diagnosis and at the start of each aHUS recurrence, and complement regulatory protein test results.

During the 30-Day-Pre-Treatment Period and Treatment Period, the following information was collected:

- start date of the most recent aHUS episode, and clinical signs and symptoms associated with the episode
- concomitant treatment/medications taken for aHUS or related to eculizumab administration
- date of meningococcal vaccine administration
- PT dates and type of PT
- renal replacement therapy, type, frequency and start/stop date, if applicable

- kidney transplantation or nephrectomy, if applicable
- number and duration of hospitalizations related to the current aHUS episode
- major vascular events
- available chemistry (BUN, creatinine, glucose, ALT, AST, LDH, total bilirubin, albumin, total protein, uric acid, estimated GFR), hematology (WBC, RBC, neutrophil count, platelet count, hemoglobin, hematocrit, reticulocytes, schistocytes), urinalysis and urinary creatinine and protein, haptoglobin, plasma d-dimer, and complement markers.
- eculizumab administration date, time and dosage
- body weight, height and blood pressure at the beginning of the treatment and on the dates of eculizumab administration
- adverse events causally related to eculizumab and pre-specified adverse events of special interest (regardless of causal association with eculizumab). A summary of all adverse events was also collected without assessment of severity or relationship
- available PK, PD, or human anti-human antibody assessments
- when applicable, information relating to patient death.

During the Post Treatment Period, the following information was collected:

- adverse events causally related to eculizumab and pre-specified adverse events of special interest (regardless of causal association with eculizumab) were collected up to eight weeks following the last eculizumab dose.
- time to first recurrence of aHUS following the last eculizumab treatment, and criteria for diagnosis of the recurrence
- reason for eculizumab discontinuation (and reason for restarting eculizumab, if applicable)

For all patients included in the trial, the treating physician filled out a safety assessment form which indicated if the patient developed an adverse reaction to eculizumab. The safety of eculizumab therapy was assessed by examination of any recorded adverse events, laboratory abnormalities, and pre-specified adverse events of special interest. The study report indicates that all adverse events were systematically collected regardless of the causal relationship with eculizumab. However information about serious adverse events was not collected during the retrospective data collection.

Adverse events of "special interest" included: meningococcal infection, serious infections, death, serious hemolysis after drug discontinuation, pregnancies, serious infusion reactions, immunogenicity and malignancies.

Reviewer note: the Applicant stated that they did not collect information regarding serious adverse events (SAEs) because they were already included in periodic safety update reports to the FDA.

Adult and adolescent patients weighing at least 40 kg received were treated using the same dosage regimen for eculizumab that was used in the prospective studies (C08-002 and C08-003). Alexion provided recommendations for weight-based dosing to the treating physicians of pediatric patients weighing less than 40 kg. These recommendations were based on PK-PD modeling.

Reviewer note: Due to the retrospective nature of this study, the actual dose administered to some patients in this retrospective study was different from dosing recommendations made by Alexion. However, the FDA Clinical Pharmacology reviewer concluded that the dosing regimen used in Study C09-001r for pediatric patients weighing less than 40 kg was not materially different from the pediatric dosage regimen proposed for the Soliris label by the Applicant.

5.3.3.4 Statistical Plan for Study C09-001r

Descriptive statistics of efficacy parameters were presented for the 30-day Pre-Treatment and Treatment period. The efficacy outcomes assessed in Study C09-001r were the same as the parameters assessed in the prospective studies, based on the data that was available for each patient.

6 REVIEW OF EFFICACY

Efficacy Summary

The primary assessment of the efficacy of eculizumab for the treatment of adult and adolescent patients is based upon analysis of data from two single arm prospective studies, Studies C08-002 and C08-003. Multiple endpoints related to thrombotic microangiopathy were measured in these studies. These endpoints evaluated changes in laboratory markers of thrombotic microangiopathy (e.g., platelet counts and LDH), changes in dialysis requirements, the need for additional plasma therapy after eculizumab was started, and changes in renal function markers, such as glomerular filtration rate.

Because thrombocytopenia experienced by patients with aHUS does not typically result in abnormal bleeding, changes in hematologic parameters provide supportive evidence that eculizumab decreases the extent of thrombotic microangiopathy occurring during an aHUS exacerbation, but do not signify a material clinical benefit to patients. The major morbidity experienced by patients with aHUS is deterioration of renal function. Therefore, analysis of improvement in renal function conferred by eculizumab, as evidenced by decrease in requirement for dialysis, provides the most concrete evidence that eculizumab provides clinical benefit to patients. Improvements in estimated

glomerular filtration rate (eGFR) provide supportive evidence that eculizumab mitigates or improves acute renal damage caused by thrombotic microangiopathy in aHUS. Analysis of other descriptive endpoints, including hematologic normalization, platelet count change from baseline, TMA event-free status, and TMA-intervention rates provide additional supportive evidence of an effect on eculizumab therapy on markers of thrombotic microangiopathy.

The efficacy assessment was complicated by the small numbers of patients, the lack of a comparator arm, and the heterogeneity of the patient population enrolled in the trials submitted to support this application. The assessment of the treatment effect of eculizumab in pediatric patients was particularly challenging; the bulk of pediatric data was derived from a retrospective study (Study C09-001r) of a heterogeneous group of patients with varying degrees of aHUS-related morbidity. FDA statistical reviewers did not cite major statistical concerns with this application, other than the limitations inherent in single arm studies of small numbers of patients.

The limitations of the studies supporting this application primarily stem from the rarity of aHUS. Given the low prevalence of this disease, it is unlikely that it would be feasible to conduct an adequately powered randomized controlled trial. Additional challenges to the conduct of a randomized controlled trial in aHUS include the lack of approved therapeutic alternatives, absence of rigorously studied assessments of the effect of plasma therapy on the clinical outcomes of patients with aHUS, and the inconsistent approach to treatment of aHUS. This reviewer acknowledges that the limitations of these studies necessitate the application of regulatory flexibility and clinical judgment in making a determination regarding whether there is sufficient evidence to support the approval of eculizumab for the treatment of aHUS. However, recognizing the challenges inherent in conducting studies of rare diseases and the complexity of a risk/benefit analysis of drugs used to treat these diseases, the Agency has historically exercised regulatory flexibility in evaluating applications of drugs used to treat rare, serious illnesses.

21 CFR Part 314 Section 314.126 states that adequate and well controlled studies provide the primary basis for determining whether **there is "substantial evidence"** to support claims of effectiveness. Although these regulations pertain to drugs, the FDA guidance, entitled *Guidance for Industry: Providing Clinical Evidence of effectiveness for Human Drug and Biological Products*, indicate that the same concept applies to biologics. The characteristics of a well-controlled study include:

1. a clear statement of study objectives and proposed methods of analysis
2. *a study design that permits a valid comparison with a control to provide a quantitative assessment of drug effect*
3. the method of selection of subjects provides adequate assurance that they have the disease being studied

4. *the method of assigning patients to treatment and control groups minimizes bias, and adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data*
5. the methods of assessment of **subjects' response are well-defined and reliable**; and there is an analysis of the results of the study adequate to assess the effects of the drug.

The prospective studies, Study C08-002 and C08-003, clearly meet the first, third, and fifth criteria. Due to the single-arm nature of the studies, it is less clear if the studies fulfill the second and fourth criteria (in italics). The regulations indicate that the Agency may waive some of the requirements of a well-controlled study in its determination of whether there is substantial evidence to support an efficacy claim. However, if the definition of historical control outlined in the regulations is interpreted broadly, then these criteria are also met. In these studies, each patient served as their own historical control. The pre-treatment history captured in the studies documented dialysis requirements, plasma therapy administered, and markers of renal function and thrombotic microangiopathy prior to treatment with eculizumab. Because it may reasonably be assumed that patients experiencing an aHUS exacerbation will not spontaneously improve in the absence of an effective therapy, documented improvements in these parameters can reasonably be attributed to eculizumab.

Additionally, the application provided historical information regarding outcomes of patients with aHUS which may serve as a comparator. There is limited published literature to provide the basis for a comparison with a historical control. However, two cohort studies (Sellier-Leclerc 2007 August 18(8):2392-400 J am Soc Nephrol and Caprioli J et al 2006 Blood Aug 15; 108(4):1267-79) provide insight regarding outcomes of patients with aHUS who are treated with supportive care or plasma therapy. In the first study, six months following the treated aHUS episode, 2/22 patients (9%) who received plasma therapy died, 7/22 (32%) had end stage renal disease, and 5/22 (23%) had a recurrent exacerbation. Death and ESRD occurred with a similar frequency in the group of patients who did not receive plasma therapy (2/23 or 9%, and 9/23 or 39%, respectively). In the Caprioli cohort of 144 patients with aHUS, 85% of patients were treated with plasma therapy. After 24 months of follow up, 18% of patients died, and 35% had end stage renal disease or a dialysis requirement. Seventy percent of the patient deaths and development of requirement for dialysis occurred within the first six months.

Efficacy data from Study C08-002, which enrolled patients with aHUS resistant to plasma therapy, provide the strongest evidence that eculizumab provides clinical benefit to patients by improving renal function. Of the five patients who required dialysis within one week prior to starting eculizumab, four patients discontinued dialysis after eculizumab was initiated. Additionally, by the time of data cut-off, nine of 17 patients (53%) exhibited improvement in estimated glomerular filtration rate by more than 15 ml/min/1.73 m². In these nine patients, the median improvement was 48

mL/min/1.73m² (range: 20, 119 ml/min/1.73 m²), and the median duration of improvement was 249 days (168-392 days). Patients enrolled in Study C08-003, who tended to have a more long-standing history of aHUS, exhibited more subtle improvement in renal function. In Study C08-003, the median change in eGFR was 5 ml/min/1.73 m² (range: -1 to 20), and one patient exhibited an improvement in eGFR by more than 15 ml/min/1.73 m². No change in the requirement for chronic dialysis was observed in this study.

The differences in the magnitude of impact of eculizumab on parameters of renal function are likely to be due to differences in the aHUS-related characteristics of patients enrolled in the two studies. Study C08-002 enrolled patients more recently diagnosed with aHUS who were not exhibiting sufficient improvement with plasma therapy for an acute aHUS exacerbation; these patients were more likely to have acute renal injury that was more amenable to reversibility. In contrast, patients enrolled in Study C08-003 tended to have a longer history of aHUS, and prolonged impairment of renal function. In addition, patients enrolled in Study C08-003 were permitted to have a chronic dialysis requirement. Therefore, patients enrolled in Study C08-003 were more likely to have had longstanding renal damage that was less amenable to improvement. Based on analysis of these studies, it appears that eculizumab treatment resulted in improved renal function in patients who had acute renal damage, and maintenance of renal function in patients with chronic renal impairment. No patient deaths occurred in either study, after more than six months of follow up. Overall, the outcomes of patients enrolled in these studies compare favorably with the patient outcomes in the Sellier-Leclerc and Caprioli and cohort studies described above.

The primary assessment of efficacy of eculizumab in the treatment of aHUS in children is based on analysis of data from nineteen children enrolled in a single retrospective study, Study C09-001r. Overall, the efficacy results for these pediatric patients appeared consistent with what was observed in patients enrolled in Studies C08-002 and C08-003. A total of 7 of 19 pediatric patients (37%) experienced an improvement in eGFR of at least 15 mL/min/1.72 m² that lasted a minimum of 28 days during the treatment period. In these patients, the eGFR improvement was sustained through the end of the study period and the median change from baseline was 40 ml/min/1.73 m² (range: 21 to 93 ml/min/1.73 m²).

The efficacy of eculizumab for the treatment of pediatric patients with aHUS is also supported by the findings of the prospective studies in adult and adolescent patients. The FDA guidance, entitled *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, referencing 21 CFR 201.57 (f) (9) (iv), describes circumstances in which pediatric use information may be included in labeling of products approved for use in adults in the absence of controlled clinical trials in children. In such cases, the applicant must provide information to support pediatric use, and the Agency must “conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit

extrapolation from adult efficacy **data to pediatric patients.**" In this application, the applicant provides information to substantiate that the pathophysiology and clinical course of aHUS in adults and children are similar, and the findings of Study C09-001r are consistent with the findings in the prospective studies in adolescent and adult patients.

Analysis of additional endpoints for all three studies provide supportive evidence that eculizumab ameliorates the signs of thrombotic microangiopathy, stabilizes or improves renal function, and obviates the requirement for plasma therapy in patients with aHUS.

6.1 Indication

Alexion proposed the following new indications for eculizumab in this sBLA submission:

Soliris is a complement inhibitor indicated for the treatment of patients with atypical hemolytic uremic syndrome.

6.1.1 Methods

To assess the effectiveness of eculizumab for the treatment of aHUS in adults, this review focuses on the efficacy results of the two prospective single-arm studies, C08-002 and C08-003, submitted in this sBLA. These studies examined the safety and efficacy of eculizumab in the treatment of patients with aHUS experiencing differing responses to plasma therapy (PT). Study C08-002 enrolled patients with PT-resistant aHUS, and Study C08-003 enrolled patients with PT-sensitive aHUS. For details regarding the FDA statistical analysis of efficacy data submitted with this sBLA, please refer to the statistical review conducted by Kyung Lee and Mark Rothmann. Sections 5.3.1 and 5.3.2 provide summaries of the study design and statistical analysis plans for Studies C08-002 and C08-003, respectively. Briefly, both studies examined efficacy endpoints relating to thrombotic microangiopathy, including changes in hematologic parameters (platelet count, LDH), renal function markers, dialysis requirements, or need for plasma therapy.

To assess the efficacy of eculizumab for the treatment of aHUS in adults, this review focuses on analysis of data from the retrospective study (C09-001r), which included 19 pediatric patients below the age of 18.

The primary efficacy endpoint designated in each study protocol differed. However, the statistical analysis plans for the studies did not pre-specify a hierarchical plan for hypothesis testing with an alpha adjustment for multiple comparisons. Furthermore, as described in Sections 5.3.1, 5.3.2, and 5.3.3, the final efficacy analysis for each study deviated from the initial statistical analysis plan based upon interaction with the FDA

and other regulatory agencies prior to the sBLA submission. Therefore, the FDA review of clinical efficacy will focus on the following key measures of effectiveness for Studies C08-002, C08-003, and C09-001r separately:

- Change in renal function, as measured by:
 - change in dialysis requirements,
 - estimated glomerular filtration rate (eGFR), and an indicator of renal function.
- 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 intervention rate (*defined as the number of plasma therapy interventions and new or increased frequency of dialyses required per patient per day*).

In addition, because the studies lack a comparator arm, this review will employ only descriptive statistics to analyze efficacy results. Case narratives were reviewed in detail, and summaries of patient outcome are also provided in this review.

A brief discussion of supportive analyses of other efficacy endpoints and indicators of TMA activity is presented in Sections 6.5.

6.2 Study C08-002: aHUS Resistant to Plasma Therapy

6.2.1 Study C08-002 Demographics

Table 12 shows the baseline demographics and disease-related characteristics of subjects enrolled in Study C08-002. The majority of patients were White, and women outnumbered men. One adolescent patients enrolled in Study C08-002.

Table 12: Baseline Demographic Characteristics of Patients Enrolled in Study C08-002

Patient Characteristics	Study C08-002 N = (17)
Age	
Median years of age (range)	28 (17; 68)
Adult, n (%)	16 (94)
Adolescent (12 to < 18 years), n (%)	1 (6)
Gender (n, %)	
Female	12 (71)
Male	5 (29)
Race (n, %)	
White	15 (88)

Patient Characteristics	Study C08-002 N = (17)
Black	1 (6)
Asian	1(6)

Table 13 provides a summary of pertinent historical data related to the aHUS diagnosis and prior aHUS experience in patients enrolled in Study C08-003. The majority of patients had at least one previous exacerbation prior to enrollment, and 41% of patients had received at least one prior renal transplant due to end stage renal disease from prior exacerbations. A complement regulatory factor (CRF) mutation or autoantibody was identified in 76% of patients. Factor H mutations were the most common type of CRF mutation identified.

Table 13: Summary of aHUS Disease History of Patients Enrolled in Study C08-002

Characteristic	Study C08-002 N = (17)
Time from aHUS diagnosis to screening	
median months (range)	9.7 (0.3, 236)
Prior renal transplant, n (%)	7 (41)
First aHUS exacerbation	7 (41)
At Least one known CRF mutation or auto-antibody, n (%)	13 (76)
Multiple CRF mutations or auto-antibodies, n (%)	4 (24)
Type of CRF abnormality, n (%)	
Factor H mutation	4 (24)
Factor H mutation with CRF mutation	2 (12)
Factor I Mutation	3 (18)
MCP Mutation	1 (6)
Anti-factor H antibody with CRF mutation	2 (12)
C3 Mutation	1 (6)

Abbreviation: CRF: Complement Regulatory Factor

Table 14 provides a summary of the key characteristics of the current aHUS exacerbation leading to treatment and baseline laboratory parameters of patients enrolled in Study C08-003. Consistent with the eligibility criteria for this study, patients generally had platelet counts below $150 \times 10^9/L$ prior to enrollment. Additionally, compared to Study C08-003, the time from onset of the current exacerbation to enrollment was shorter (0.75 months versus 8.6 months in Study C08-003). Compared to Study C08-003, patients enrolled in Study C08-002 received a higher median number of plasma therapy treatments the week prior to enrollment (6 versus 1.5 in Study C08-003).

Table 14: Key Characteristics of Current aHUS Exacerbation and Baseline Laboratory Parameters of Patients Enrolled in Study C08-002

Characteristic	Study C08-002 N = (17)
<u>Current Exacerbation</u>	
Time from onset of current exacerbation to screening, median months (range)	0.75 (0.23, 3.70)
No. PT sessions administered, median (range)	17 (2, 37)
No. PT sessions the week prior to first eculizumab dose, median (range)	6 (0, 7) ¹
Proportion of patients requiring dialysis at study entry, n (%)	5 (29)
<u>Baseline Laboratory Parameters</u>	
Platelet Count ($\times 10^9/L$), median (range)	118 (62, 161)
LDH (U/L), median (range)	269 (134, 634)
Creatinine ($\mu\text{mol/L}$), median (range)	256 (124, 787)
eGFR range ($\text{ml/min}/1.73 \text{ m}^2$), n(%)	
<15 (Kidney failure)	7 (41)
15-29 (CKD4) (Severe)	5 (29)
30-59 (CKD3) (Moderate)	5 (29)
60 or higher	0 (0)

¹ Patient 197-001 did not receive plasma therapy the week prior to enrollment due to an allergic reaction.
 Abbreviation: PT: plasma therapy

All patients received concomitant therapy while being treated with eculizumab. The following types of concomitant medications were used by over half of the patients enrolled in Study C08-002 (in descending order, by frequency):

- Vaccinations, including the meningococcal vaccine: (100%)
- Systemic antibacterial agents (94%)
- Calcium channel blockers (88%)

- Agents acting on the renin-angiotensin system (82%)
- Beta blocking agents (82%)
- Diuretics (82%)
- Other antihypertensives (76%)
- Analgesics (76%)
- Antianemic preparations (76%)
- Systemic corticosteroids (71%)
- Drugs for acid-related disorders (71%)

The majority of patients received erythropoietin stimulating agents. 8 (47%) received darbepoetin alfa, 2 (12%) received epoetin alpha, and 1 (6%) received epoetin beta.

6.2.2 Subject Disposition

Seventeen patients enrolled in Study C08-002 and received treatment. At the time of data-cut off, 13 (76%) patients had completed the 26 week treatment period and continued to receive eculizumab. Of the four patients who discontinued eculizumab, two patients (patients 2-141-001 and 2-198-001) completed 26 weeks of eculizumab therapy but opted not to enroll in the extension period. One patient (2-140-001) **discontinued eculizumab due to an "adverse event", and another patient (2-043-001) withdrew from the study following receipt of a single dose of eculizumab after being diagnosed with systemic lupus erythematosus.**

6.2.3 Analysis of Key Endpoint(s) in Study C08-002 (Plasma Therapy Resistant aHUS)

Four of the five patients who required dialysis at study entry permanently discontinued dialysis for the duration of Soliris treatment, and one patient developed a new dialysis requirement.

Table 15 summarizes the key efficacy results for Study C08-002.

Table 15: Efficacy Results for Study C08-002 in Plasma Therapy-Resistant aHUS

Efficacy Parameter	Study C08-002 N=17
Hematologic normalization ¹ , n (%)	13 (76)
Median duration of hematologic normalization, weeks (range) ¹	37 (25, 62)

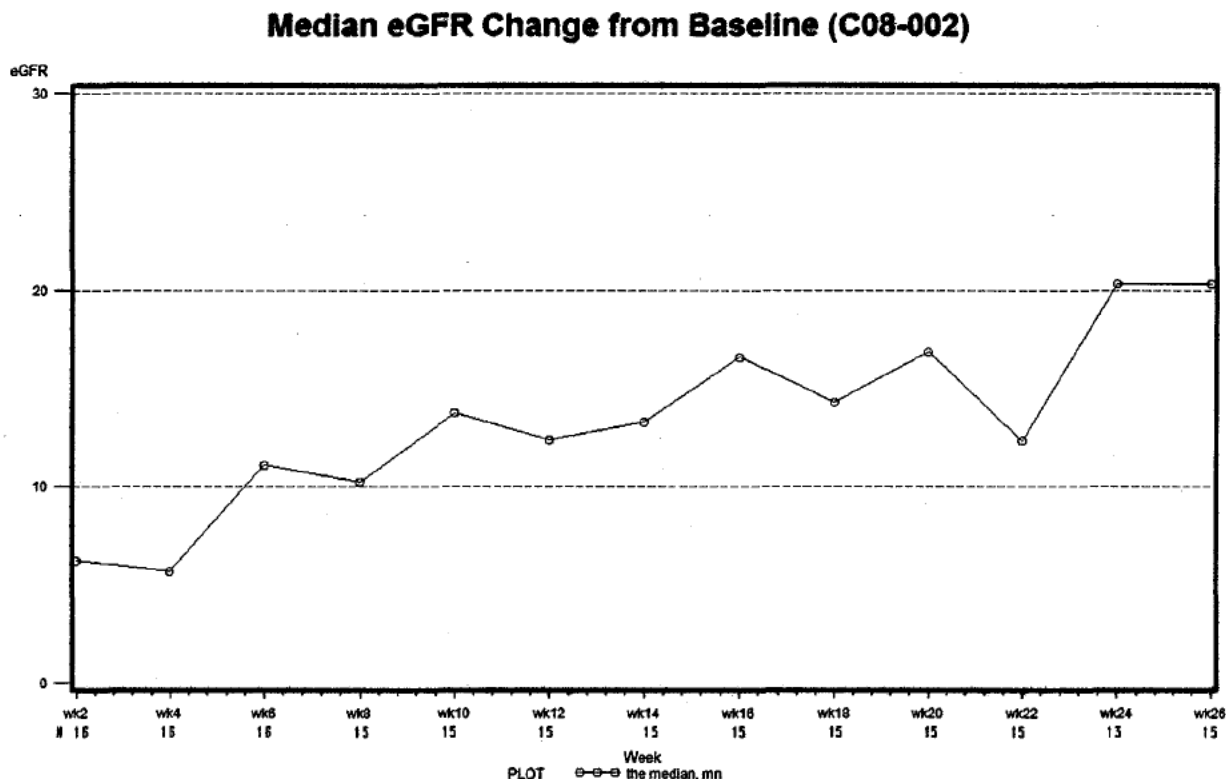
Efficacy Parameter	Study C08-002 N=17
Complete TMA response, n (%) (95% CI)	11 (65)
Median duration of complete TMA response, weeks (range) ¹	38 (25, 56)
Daily TMA intervention rate, median (range)	
Before eculizumab	0.88 (0.04, 1.59)
On eculizumab treatment	0 (0, 0.31)
Change in eGFR (mL/min/1.73 m ²) at 26 weeks, median (range)	+20 (-1-98)
eGFR improvement $\geq$ 15 mL/min/1.73 m ² , n (%) ¹	9 (53)
Median eGFR improvement, mL/min/1.73 m ² (range) ²	48 (20, 119)
Median duration of eGFR improvement, days (range) ²	251 days (28-392 days)

¹At data cut-off (September 8, 2010).

²observed at data cut-off (September 8, 2010) in the 9 subjects with eGFR improvement of $\geq$ 15 mL/min/1.73 m².

Figure 3 provides a graphic representation of the median change in eGFR from baseline (mL/min/1.73 m²) starting at Week 2 of eculizumab therapy. This figure illustrates that median eGFR improved starting as early as week 2, and that improvements in eGFR were generally sustained throughout the twenty-six week treatment period.

Figure 3: Median eGFR Change from Baseline in Study C08-002



Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

6.2.4 Analysis of supportive efficacy data for Study C08-002 (Plasma Therapy Resistant aHUS)

The applicant provided analyses of changes in laboratory markers of hemolysis and microangiopathy to provide supportive evidence that eculizumab decreases TMA activity in patients with aHUS.

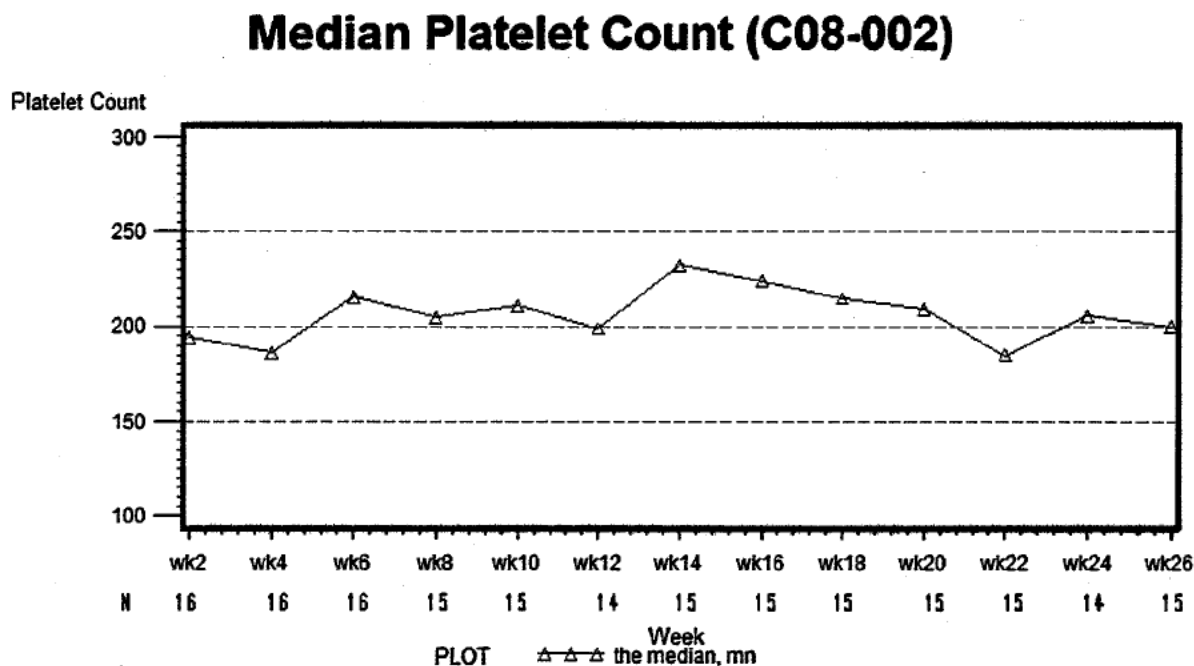
Platelet Count Change from Baseline

Platelet count, a marker of thrombotic microangiopathy, was monitored every one to two weeks during the treatment phase of Study C08-002. The applicant calculated the platelet count change from baseline at each post-dose day of measurement, after Day 4 through Week 26 using a repeated measurement ANOVA model. The point estimate change from baseline through 26 weeks was $72.7 \times 10^9/L$ (95% CI: 40.1 – 105.2).

The median platelet count at baseline for subjects enrolled in Study C08-002 was $118 \times 10^9/L$ (range: 62, 161). Figure 4 provides a graphic representation of the median

platelet count ($\times 10^9/L$) starting at Week 2 of eculizumab therapy. This figure illustrates that the median platelet count rose by Week two of therapy, and that this rise was generally sustained throughout the 26 week treatment period.

Figure 4: Median Platelet Counts in Study C08-002



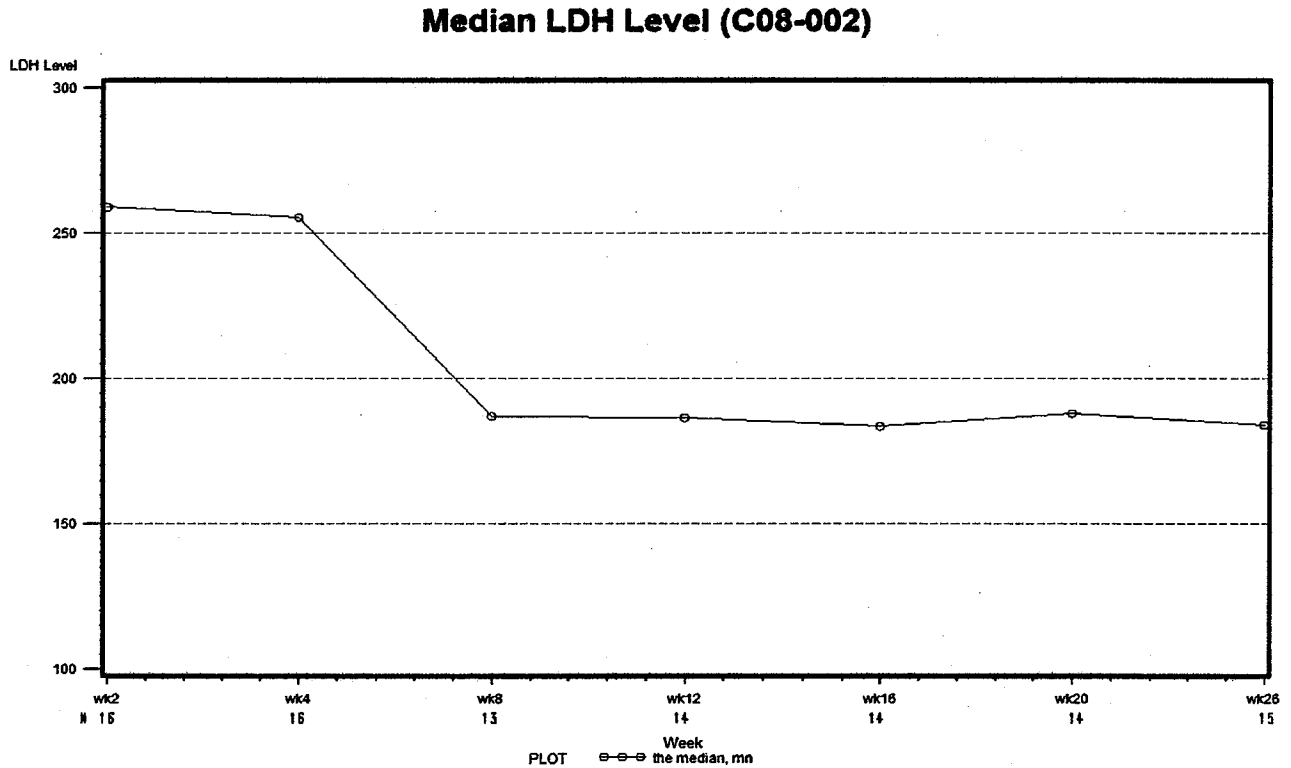
Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

Change in LDH levels from baseline

Lactate dehydrogenase (LDH), a marker of hemolysis and thrombotic microangiopathy, was measured at regular intervals during the treatment phase of Study C08-002.

Ten patients (59%) had an elevated LDH at the time of the diagnosis of the current aHUS episode. The median LDH at baseline for subjects enrolled in Study C08-002 was 269 U/L (134, 634). Figure 5 provides a graphic representation of the median LDH (in U/L) starting at Week 2 of eculizumab therapy. This figure illustrates that the median LDH declined substantially by Week 8, and remained below the baseline levels for the duration of therapy.

Figure 5: Median Serum LDH Levels in Study C08-002



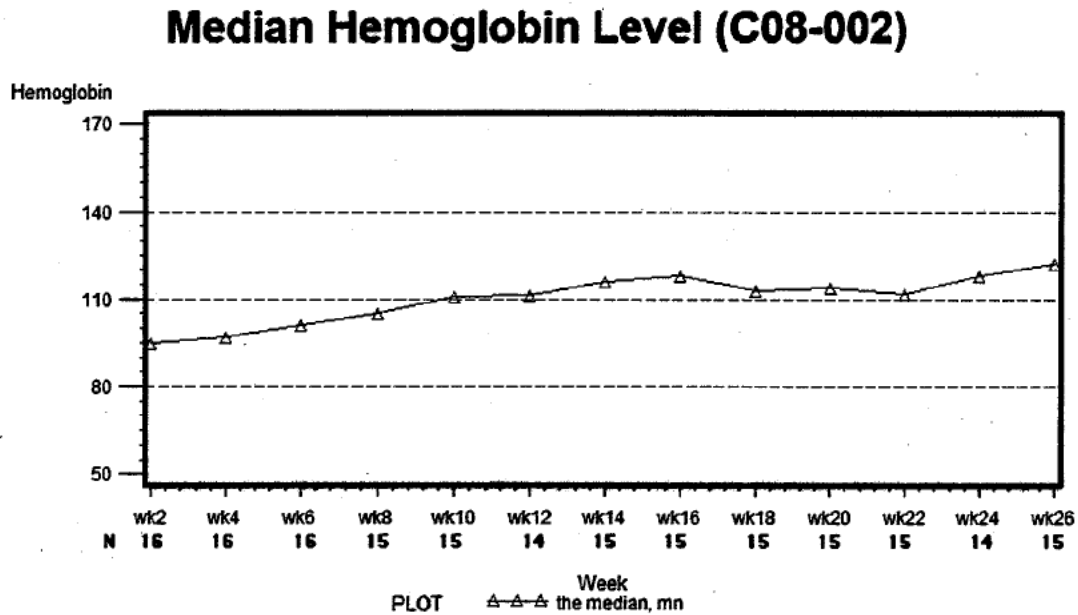
Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

Change in Hemoglobin from Baseline

Hemoglobin levels were monitored every one to two weeks during the 26 week treatment phase of Study C08-002. Eleven patients (65%) exhibited an increase in hemoglobin by at least 2 g/L that lasted a minimum of 4 weeks during the 26-week treatment period. Figure 6 provides a graphic representation of the median hemoglobin level (in g/L) starting at Week 2 of eculizumab therapy. This figure illustrates that median hemoglobin levels rose from Week 2 to Week 12 of therapy.

It is difficult to assess the contribution of eculizumab in the improvement of anemia due to confounding factors. The majority of patients were treated with erythropoietin stimulating agents prior to and during the study. Additionally, one patient received a transfusion of packed red blood cells (PRBCs) prior to starting eculizumab, and six patients received transfusions of PRBCs or whole blood during the study. In the majority of cases, these transfusions occurred during the first two weeks of study therapy. One patient (2-041-001) received six PRBC transfusions between study day 12 and 71.

Figure 6: Median Hemoglobin Levels in Study C08-002

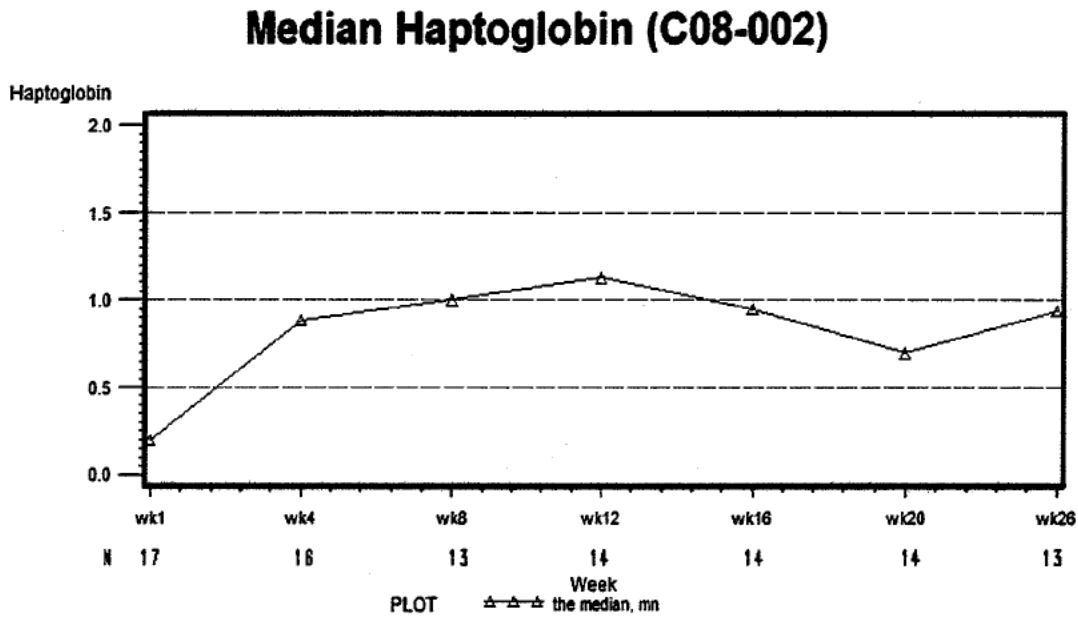


Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

Change in Haptoglobin from Baseline

Haptoglobin levels, which decrease with intravascular hemolysis, were monitored every one to four weeks during the 26 week treatment phase of Study C08-002. Figure 7 provides a graphic representation of the median haptoglobin level (in g/L) starting at Week 2 of eculizumab therapy. This figure demonstrates that median haptoglobin approximately tripled by Week 4, and remained increased through week 26.

Figure 7: Median Haptoglobin Levels in Study C08-002



Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

6.2.5 Narrative Summaries for Patients Enrolled in Study C08-002

Table 16 provides a brief summary of key characteristics and outcomes for patients enrolled in Study C08-002. Entries for patients who discontinued dialysis during the eculizumab treatment period are shaded in gray.

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Table 16: Patient Summaries for Study C08-002.

ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant/dialysis ¹	Hematologic normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
029-001	17	CFH	1	N/N	Y/Y/Y	TMA event free status maintained as of data cut-off date; remained on eculizumab therapy. Creatinine decreased by more than 50% from baseline and stabilized just above normal levels.
039-001	47	CFH, CFI, CFHR 3- CFHR1	2	Y/N	Y/Y/Y	Second aHUS exacerbation occurred one month following kidney transplant, prior to eculizumab therapy. Exhibited hematologic normalization and complete TMA response from Day 140 of therapy, which were sustained at data cut-off. TMA event free status for 448 days (sustained as of data cut-off date). <i>Platelet count 93-143 X 10⁹/L the week prior to eculizumab while receiving PT. Creatinine decreased by approximately 25% on eculizumab therapy.</i>
040-001	47	CFH	1	Y/Y	Y/Y/Y	Continued to require dialysis throughout treatment period. Periods of decrease in creatinine levels by 25% or more but generally remained elevated. No improvement in eGFR. <i>Interpretation of</i>

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant/dialysis ¹	Hematologic normalization ² / Complete-TMA response ³ / TMA event-free ⁴	Notes
						<i>TMA response not relevant due to ongoing dialysis requirement. TMA event free status achieved (no increase in dialysis requirement or PT therapy).</i>
041-001	21	N	1	Y/N	Y/Y/Y	Patient remained on eculizumab at data cutoff with sustained Hematologic Normalization, Complete TMA response, and event-free status. Greater than 50% decrease in creatinine from baseline.
043-001	26	N	0	N/N	N/N/N	<i>SLE diagnosed after one eculizumab dose administered; patient withdrawn from study.</i>
045-001	20	CFI	1	N/N	Y/Y/Y	Platelet count remained above 150 after 3 rd eculizumab dose. LDH normalized after fourth dose. Creatinine decreased by 43%. Remained on eculizumab at data cut-off and TMA event free status sustained for 269 days.
045-002	31	Anti Factor H antibody, CRHR3-CRHR1 mutation	1	N/N	Y/N/Y	Creatinine remained elevated on eculizumab.

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant/dialysis ¹	Hematologic normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
070-001	38	CFI	0	Y/Y	Y/Y/Y	Dialysis discontinued 14 days after starting eculizumab. As of data cut-off date, TMA event free for 338 days.
110-001	25	CFH	0	N/Y	Y/Y/Y	Discontinued dialysis after eculizumab started. TMA event free for 447 days at data cut-off.
140-001	39	CFH, CFHR1-CFHR-3	2	Y/N	N/N/N	Eculizumab discontinued after the fourth dose due to worsening renal function and pancytopenia. Dialysis initiated.
141-001	21	MCP	1	N/N	Y/Y/Y	Completed 26 week treatment period and did not continue into extension period. Creatinine normalized following the 3 rd eculizumab dose. EGFR also increased by 119 ml/min/1.73 m ² . TMA event-free status was achieved for 237 days.
*191-001	22	Gain of Function CF3	4	N/Y	Y/Y/Y	Platelet count and LDH were normal prior to eculizumab, but hemoglobin was low (8 g/L). Dialysis discontinued after Day 6 of eculizumab therapy. Creatinine decreased by > 50% and approached ULN. <i>In this patient's case, hematologic normalization reflects maintenance of normal LDH and platelet parameters during this study.</i>

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant/dialysis ¹	Hematologic normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
196-001	21	N	0	N/Y	Y/Y/Y	Creatinine normalized with eculizumab and dialysis was discontinued after Day 3 of eculizumab therapy. TMA event-free status was achieved for 264 days and was sustained as of the data cut-off.
197-001	28	N	1	Y/N	Y/N/Y	<i>LDH was within normal range and platelets were close to normal range (146 X 10⁹/L) prior to initiation of eculizumab; therefore, hematologic normalization reflects maintenance of normal parameters in this patient.. Creatinine and eGFR did not improve.</i>
198-001	29	CFI	0	N/N	Y/Y/Y	TMA event free for 188 days as of data cut-off. Did not enter treatment extension period. After initiation of eculizumab, creatinine normalized (decreased from 133 µmol/L at baseline to 71 µmol/L) and eGFR improved by 63 ml/min/1.73 m ² .
198-002	68	Anti-CFH antibody and CFHR1-CFHR3 mutation	0	N/Y	N/N/Y	Platelet count normalized but LDH remained slightly above normal range and creatinine levels were relatively stable. Patient discontinued dialysis 34 days prior to eculizumab therapy, and remained dialysis free. TMA event-free for 187 days at data cut-off.

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant/dialysis ¹	Hematologic normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
*205-001	40	CFH	1	Y/N	N/N/Y	Normal baseline platelet count (166) and LDH with plasma therapy; average screening platelet count was 142 X 10 ⁹ /L. Developed worsening renal function, required 3 supplemental doses of eculizumab and 5 PT sessions between day 84 and day 91 of therapy. TMA event free for 98 days thereafter.

* normal baseline platelet count.

¹ renal transplant prior to initiation of eculizumab or dialysis within 8 weeks prior to eculizumab therapy.

² Hematologic normalization was defined as normalization of platelet count and LDH defined by consecutive measurements which spanned at least four weeks.

³ Complete TMA response was defined as hematologic normalization plus improvement in renal function (at least a 25% reduction in serum creatinine by consecutive measurements spanning at least 4 weeks).

⁴ TMA Event-Free status was defined as absence for at least 12 weeks of [1] decrease in platelet count of > 25% compared to the pre-plasma therapy baseline; [2] plasma therapy while receiving eculizumab and [3] new dialysis requirement or need for increased frequency of dialysis.

Abbreviations: ID: patient ID number; CRF: Complement Regulatory Factor; aHUS: atypical hemolytic uremic syndrome; N; no; Y: yes; TMA: thrombotic microangiopathy; LDH: lactate dehydrogenase; FI: Complement Factor I; CFH: Complement Factor H; MCP: membrane cofactor protein; C3: Complement factor 3; eGFR: estimated glomerular filtration rate;

6.3 Study C08-003 aHUS Sensitive to Plasma Therapy

6.3.1 Study C08-003 Demographics

Table 17 shows the baseline demographic characteristics of patients enrolled in Study C08-003. The majority of patients were White, and women outnumbered men. Five adolescent patients enrolled in Study C08-003.

Table 17: Baseline Demographic Characteristics of Patients Enrolled in Study C08-003

Patient Characteristics	Study C08-003 N = (20)
Age	
Median years of age (range)	28 (13; 63)
Adult, n (%)	15 (75)
Adolescent (12 to < 18 years), n (%)	5 (25)
Gender (n, %)	
Female	12 (60)
Male	8 (40)
Race (n, %)	
White	17 (85)
Black	2 (10)
Other	1 (5)

Table 18 provides a summary of pertinent historical data related to the aHUS diagnosis and prior aHUS experience in patients enrolled in Study C08-003. The majority of patients had at least one previous exacerbation prior to enrollment, and 40% of patients had received at least one prior renal transplant due to end stage renal disease from prior exacerbations. A complement regulatory factor (CRF) mutation or autoantibody was identified in 70% of patients. Factor H mutations were the most common type of CRF mutation identified.

Table 18: Disease History of Patients Enrolled in Study C08-003

Characteristic	Study C08-003 N = (20)
Time from aHUS diagnosis to screening	
Median months (range)	48 (0.66, 286)
Prior renal transplant, n (%)	8 (40)

Characteristic	Study C08-003 N = (20)
First aHUS exacerbation	5 (25)
At Least one known CRF mutation or auto-antibody, n (%)	14(70)
Multiple CRF mutations or auto-antibodies, n (%)	6 (30)
Type of CRF abnormality, n (%)	
Factor H mutation	3 (15)
Factor H mutation with another CRF mutation	2 (10)
Factor I Mutation	2(10)
MCP Mutation	1 (5)
Anti-factor H antibody +/- other CRF mutations	2 (10)
Other CRF mutation(s)	4 (20)

Abbreviation: CRF: Complement Regulatory Factor

Table 19 provides a summary of the key characteristics of the current aHUS exacerbation leading to treatment and baseline laboratory parameters of patients enrolled in Study C08-003. Consistent with the eligibility criteria for this study, patients generally had normal platelet counts prior to enrollment. Additionally, compared to Study C08-002, the time from onset of the current exacerbation to enrollment was longer (8.6 months versus 0.75 months on Study C08-002). The median number of plasma therapy treatment per week prior to eculizumab treatment was 1.5.

Table 19: Key Characteristics of Current aHUS Exacerbation and Baseline Laboratory Parameters of Patients Enrolled in Study C08-003

Characteristic	Study C08-003 N = (20)
<u>Current Exacerbation</u>	
Time from onset of current exacerbation to screening, median months (range)	8.6 (1.2, 45)
No. PT sessions administered, median (range)	62 (20, 230)
No. PT sessions the week prior to first eculizumab dose, median (range)	1.5 (1, 3)
Proportion of patients requiring dialysis at study entry, n (%)	2 (10)
<u>Baseline Laboratory Parameters</u>	
Platelet Count ($\times 10^9/L$), median (range)	218 (105, 421)
LDH (U/L), median (range)	200 (151, 391)
Creatinine ($\mu\text{mol/L}$), median (range)	234 (106, 893)
eGFR range (ml/min/1.73 m^2), n(%) <15 (Kidney failure)	4 (20)

Characteristic	Study C08-003 N= (20)
15-29 (CKD4) (Severe)	6 (30)
30-59 (CKD3) (Moderate)	8 (40)
60 or higher	2 (10)

Abbreviation: PT: plasma therapy

Two patients enrolled in Study C08-003 required dialysis at study entry (patients 3-060-001 and 3-197-001). Both patients had a long-standing requirement for dialysis prior to initiating eculizumab; patient 3-060-001 had received dialysis on a chronic basis for over 15 years, and Patient 3-197-001 received dialysis two to three times per week for 6 months prior to starting eculizumab.

All patients received concomitant therapy while being treated with eculizumab. The following types of concomitant medications were used by over half of the patients enrolled in Study C08-003 (in descending order, by frequency):

- Vaccinations, including the meningococcal vaccine: (100%)
- Antihypertensives (95%)
 - Agents acting on renin-angiotensin system (85%)
 - Other antihypertensives: 35%
- Antianemic preparations (85%)
- Systemic antibacterial agents (85%)
- Beta blockers (80%)
- Calcium channel blockers (75%)
- Diuretics (70%)
- Systemic antihistamines (60%)
- Systemic corticosteroids (55%)
- Mineral supplements (55%)

The majority of patients received erythropoietin stimulating agents. 12 (60%) received darbepoetin alfa, 5 (25%) received epoetin alpha, and 1 (5%) received epoetin beta.

6.3.2 Subject Disposition

A total of 23 patients enrolled in this study, but three patients did not receive eculizumab treatment; two patients failed the screening process and one patient withdrew from the study for personal reasons prior to receiving eculizumab. The remaining 20 patients received entered the treatment period and received eculizumab. At the time of data cut-off, 19 (95%) patients had completed the 26 week treatment period and continued to receive eculizumab. Patient 3-243-001 completed the 26 maintenance treatment phase, but decided not to enroll into the extension study. Approximately eleven weeks

after discontinuing eculizumab, she developed another aHUS exacerbation, manifested by hypertension, edema, elevated creatinine, thrombocytopenia, and anemia. After eculizumab therapy recommenced, hematologic parameters resolved and renal function returned to baseline.

6.3.3 Analysis of Key Endpoint(s) in Study C08-003 (Plasma Therapy Sensitive aHUS)

Two patients enrolled in Study C08-003 had a longstanding dialysis requirement at study entry (patients 3-060-001 and 3-197-001). Patient -060-001 continued eculizumab therapy through the date of data-cutoff (on day 323 of therapy), but continued to require peritoneal dialysis. Patient 3-197-001 received a kidney transplant on Day 217, which eliminated the need for further dialysis. He remained on eculizumab and maintained renal function through data cut-off (on Day 336).

Table 20 summarizes the key efficacy findings for Study C08-003.

Table 20: Efficacy Results for Study C08-003 in Plasma Therapy-Sensitive aHUS

Efficacy Parameter	Study C08-003 N=20
Hematologic normalization ¹ , n (%)	18 (90)
Median duration of hematologic normalization, weeks (range) ²	38 (22, 52)
Complete TMA response, n (%) (95% CI) ²	5 (25)
Median duration of complete TMA response, weeks (range) ²	32 (12, 38)
Daily TMA intervention rate, median (range)	
Before eculizumab	0.23 (0.05, 1.09)
On eculizumab treatment ²	0
Change in eGFR (mL/min/1.73 m ²) at 26 weeks, median (range)	+5 (-1, 20)
eGFR improvement ≥ 15 mL/min/1.73 m ² , n (%)	1 (5)

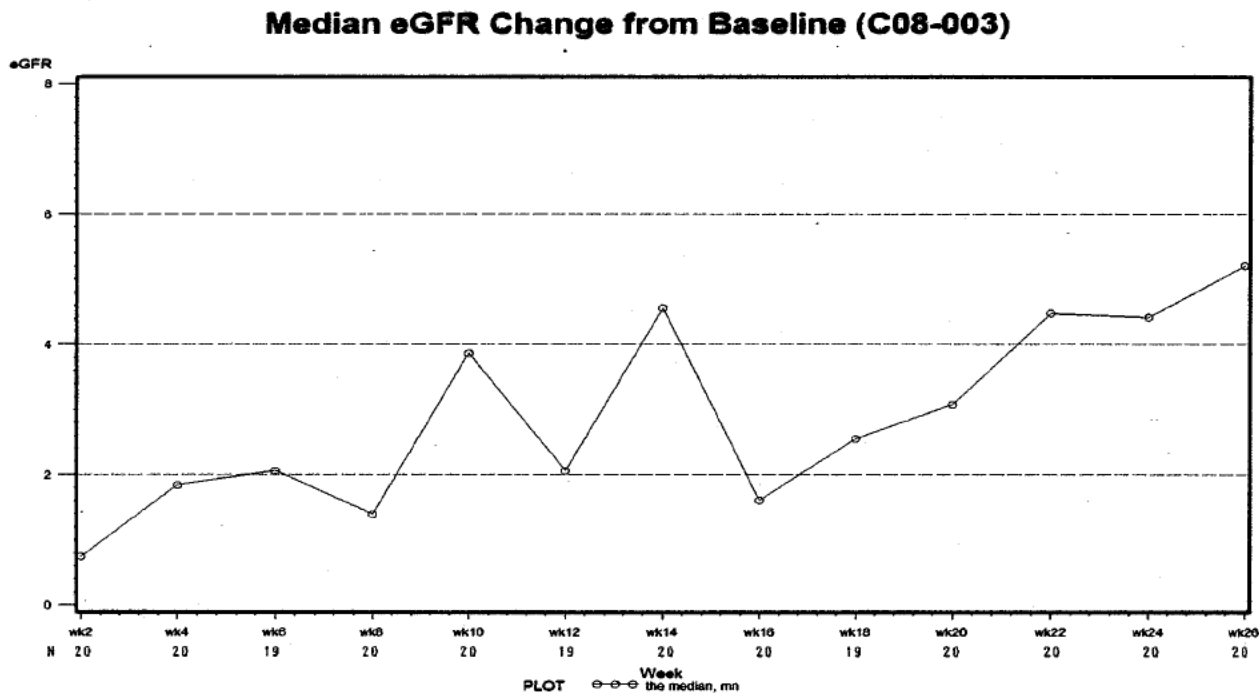
¹ In aHUS Study 2, 85% of patients had normal platelet counts and 80% of patients had normal serum LDH levels at baseline, so hematologic normalization in this population reflects maintenance of normal parameters in the absence of PT.

² At data cut-off (October 10, 2010).

In Study C08-003, renal function, as measured by median eGFR, remained relatively unchanged during Soliris therapy. Figure 8 provides a graphic representation of the

median change in eGFR from baseline (ml/min/1.73 m²) starting at Week 2 of eculizumab therapy. This figure illustrates that median eGFR remained relatively unchanged during the initial 26 weeks of treatment.

Figure 8: Median eGFR Change from Baseline in Study C08-003



Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

6.3.4 Analysis of supportive efficacy data for Study C08-003 (Plasma Therapy Sensitive aHUS)

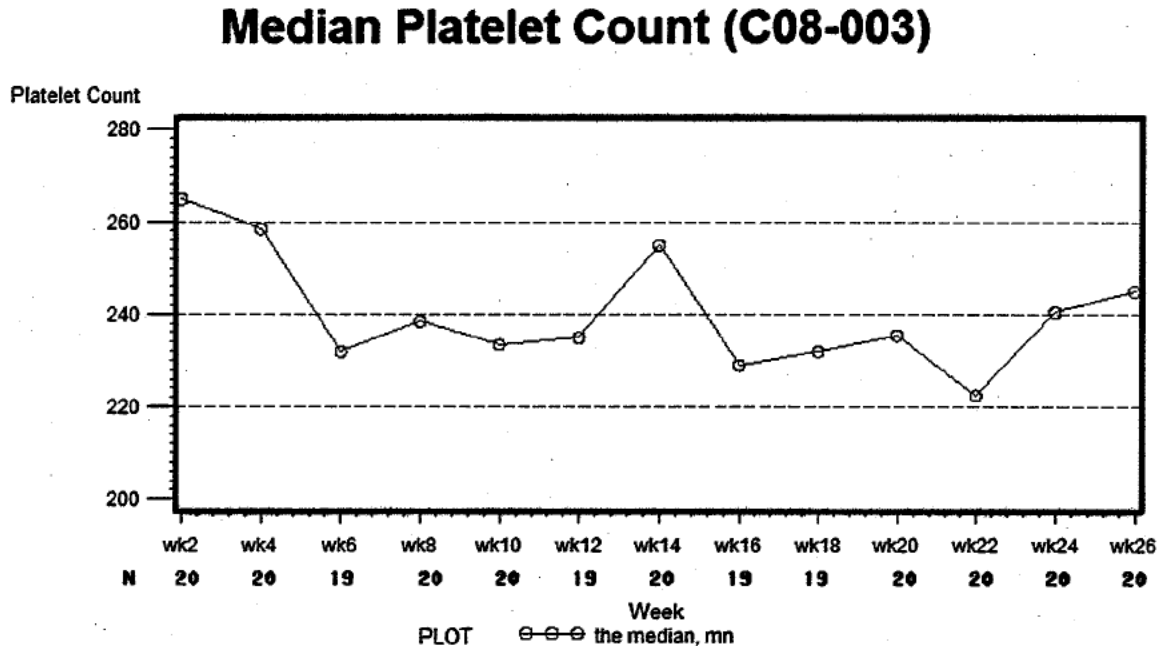
The applicant provided analyses of changes in laboratory markers of hemolysis and microangiopathy to provide supportive evidence that eculizumab decreases TMA activity in patients with aHUS.

Platelet Count Change from Baseline

Platelet count, a marker of thrombotic microangiopathy, was monitored every one to two weeks during the treatment phase of Study C08-003. As expected, because patients enrolled in Study C08-003 had **plasma therapy "sensitive" aHUS, the majority of patients (17/20, 85%) had a normal platelet count at the time of study entry.** The median platelet count at baseline for subjects enrolled in Study C08-003 was $218 \times 10^9/L$ (range: 105, 421). Figure 9 provides a graphic representation of the

median platelet count ($\times 10^9/L$) starting at Week 2 of eculizumab therapy. This figure illustrates that median platelet counts remained at or above baseline levels throughout the course of eculizumab treatment.

Figure 9: Median Platelet Counts in Study C08-003



Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

The applicant used ANOVA modeling to analyze the change in baseline platelet counts at each on-treatment day of measurement, except Days 1-4 through week 26. This analysis demonstrated that on Days 14 and 21, that the point estimate for the increase in platelet counts was $32 \times 10^9/L$ (95% CI: 9-55). At week 26, there was no material difference in the platelet counts compared to baseline.

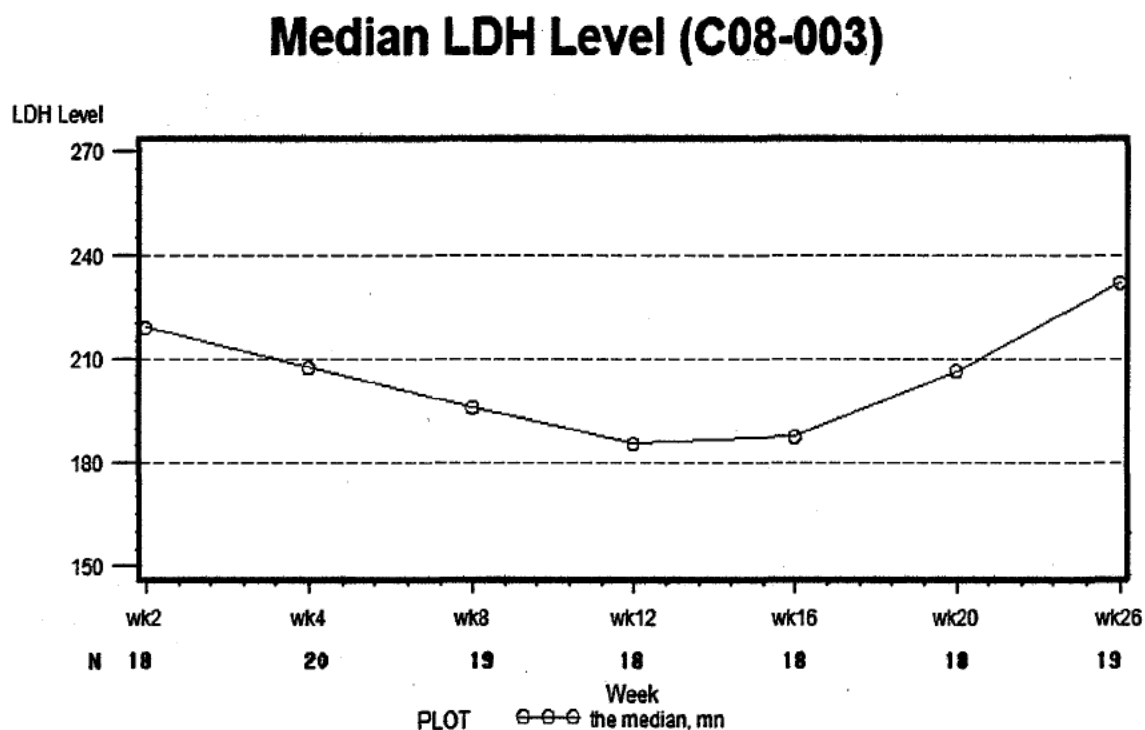
Change in LDH levels from baseline

Lactate dehydrogenase (LDH), a marker of hemolysis and thrombotic microangiopathy, was at regular intervals during the treatment phase of Study C08-003.

As to be expected, the majority of patients (16/20, 80%) had a normal LDH at the time of the study entry. The median LDH at baseline for subjects enrolled in Study C08-002 was 200 U/L (range: 151, 391). Figure 10 provides a graphic representation of the median LDH (in U/L) starting at Week 2 of eculizumab therapy. This figure illustrates

that the median LDH remained relatively stable for the duration of the 26-week treatment period.

Figure 10: Median Serum LDH Levels in Study C08-003



Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

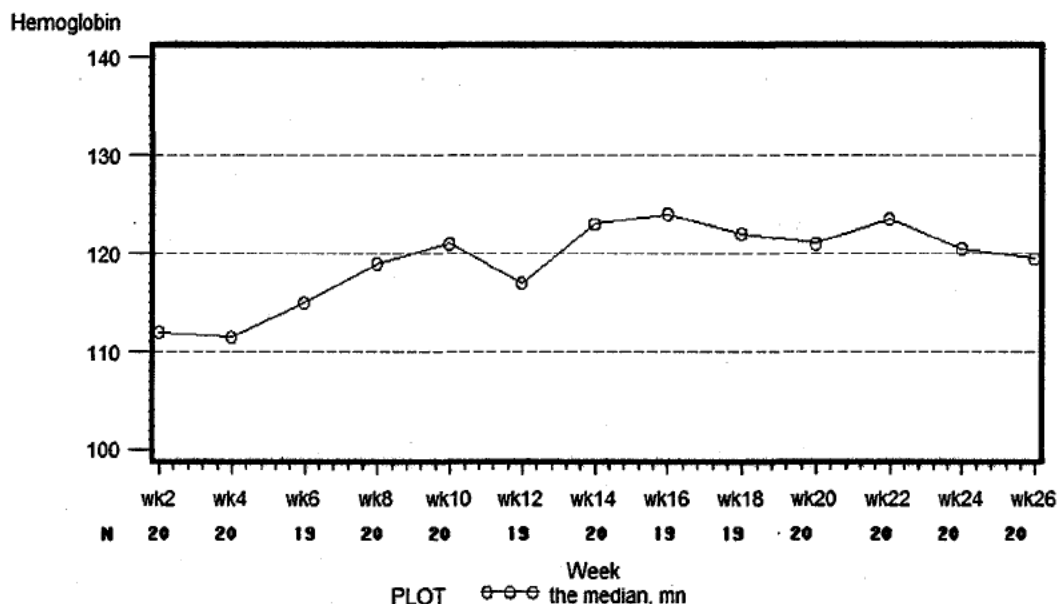
Change in Hemoglobin from Baseline

Hemoglobin levels were monitored every one to two weeks during the 26 week treatment phase of Study C08-002. Ten patients (50%) exhibited an increase in hemoglobin by at least 2 g/L that lasted a minimum of 4 weeks during the 26-week treatment period. Figure 11 provides a graphic representation of the median hemoglobin level (in g/L) starting at Week 2 of eculizumab therapy.

It is difficult to assess the contribution of eculizumab in the improvement of anemia due to confounding factors. The majority of patients were treated with erythropoietin stimulating agents prior to and during the study. Additionally, two patients received PRBC transfusions during the 2 month period prior to receiving eculizumab, and two patients received transfusions during the study period. One patient received 2 units of PRBCs on Study day 2, and another patient received one unit of platelets on Day 197.

Figure 11: Median Hemoglobin Levels in Study C08-003

Median Hemoglobin (C08-003)



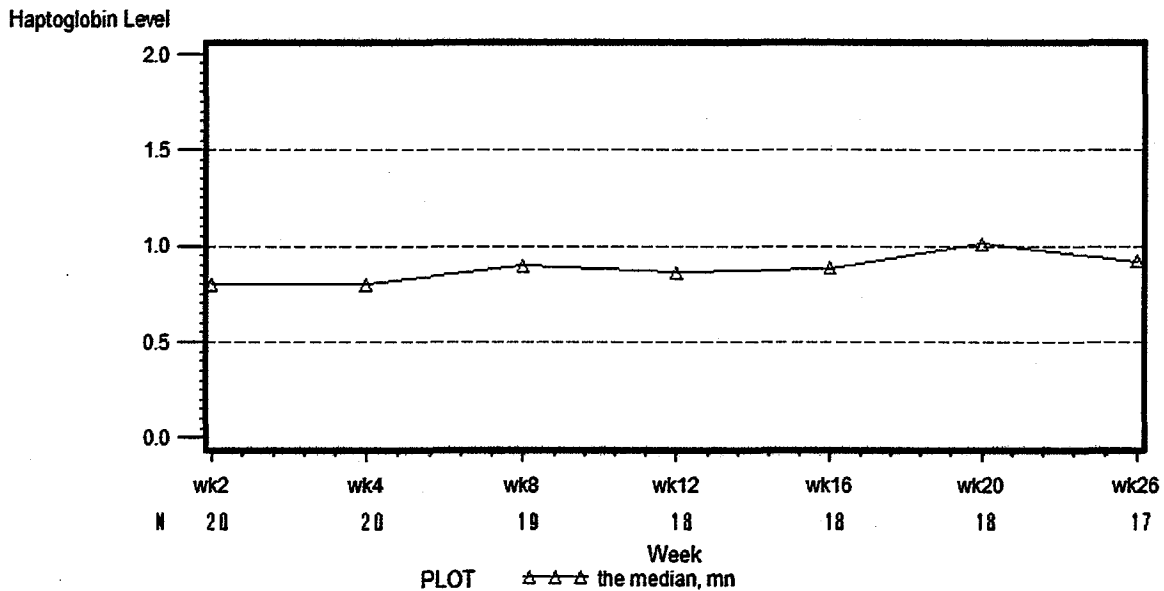
Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

Change in Haptoglobin from Baseline

Haptoglobin levels, which decrease with intravascular hemolysis, were monitored at regular intervals during the 26 week treatment phase of Study C08-002. Figure 12 provides a graphic representation of the median serum haptoglobin levels (in g/L) starting at Week 2 of eculizumab therapy. This figure demonstrates that median haptoglobin levels remained relatively stable and within the range of normal during the 26-week treatment period.

Figure 12: Median Serum Haptoglobin Levels in Study C08-003

Median Haptoglobin Level (C08-003)



Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

6.3.5 Narrative Summaries for Patients Enrolled in Study C08-003.

Table 21 provides a brief summary of key characteristics and outcomes for patients enrolled in Study C08-003.

Clinical Review
 Martha Donoghue
 sBLA 125166
 Soliris (eculizumab)

Table 21: Patient Summaries for Study C08-003.

ID	Age (yrs)	CRF Mutation	No. of aHUS episodes since diagnosis	Renal Transplant /dialysis	PT Frequency/ Type	Hemat norm ² / Complete TMA resp ³ / TMA EF ⁴	Notes
060 - 001	16	CFH	8	N/Y	Once every 2 weeks – FFP infusion	Y/N/Y	TMA event free status maintained as of data cut-off date (323 days).
060 - 002	14	Anti-CFH ab, CFHR-1-CFHR-3 mutations	0	N/N	Once every 2 weeks - FFP infusion	Y/N/Y	Creatinine remained low but stable on therapy. TMA event-free for 265 days as of data cut-off.
074 - 001	28	CFI, CD46	3	N/N	Once per week - - plasmapheresis	Y/Y/Y	Platelet counts and LDH normalized. Creatinine remained elevated but decreased by approximately 25% for over 2 months (but increased to 79% of baseline by day 308 of therapy); <i>Reviewer note: this transient improvement in creatinine does not appear to be clinically relevant.</i> TMA event free for 307 days as of data cut-off.
074 - 002	24	None	7	N/N	Once per week – plasma exchange	Y/Y/Y	Creatinine remained elevated but decreased by approximately 25% for approximately 28 days (but increased to 78% of baseline by day 308 of therapy). <i>Reviewer note: this transient improvement in creatinine does not appear to be clinically relevant.</i> TMA event free for 182 days as of data cut-off.

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ID	Age (yrs)	CRF Mutation	No. of aHUS episodes since diagnosis	Renal Transplant /dialysis ¹	PT Frequency/ Type	Hemat norm ² / Complete TMA resp ³ / TMA EF ¹	Notes
079 - 001	23	CFH, CFHR1-CFHR3	4	N/N	Twice weekly - plasma exchange	Y/N/Y	Creatinine remained stable but elevated throughout treatment. TMA event free for 181 days at data cut-off.
144 - 001	26	None	4	Y (X3)/ N	Three times per week - plasmapheresis	Y/Y/N	Creatinine decreased by approximately 30% from baseline, but remained elevated. Not TMA event free because platelet count decreased by 25% during therapy (although remained normal).
167 - 001	13	None	2	N/N	Twice per week - FFP infusion	Y/N/Y	Creatinine remained elevated but stable.
196 - 001	43	CFI	1	Y/N	Twice per week - plasma exchange	Y/N/N	Creatinine remained high but stable during eculizumab therapy. Not TMA event free because platelet count decreased by 25% during therapy (although remained normal).
196 - 002	49	None	1	Y (X2)/N	Three times per week - plasma exchange	Y/N/N	Creatinine remained elevated but stable. Not TMA event-free due to transient decreases in platelet count by 25% or more (although remained in normal range). No dialysis or plasma therapy required during eculizumab therapy.
197 - 001	50	Anti-CFH antibody	5	N/Y	Three times per week - plasma exchange	Y/N/Y	Dialysis continued during treatment period until receipt of cadaveric renal transplant during treatment extension period.
197 - 002	63	None	1	Y/N	Twice weekly - plasma exchange	Y/N/Y	TMA event free for 209 days.

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ID	Age (yrs)	CRF Mutation	No. of aHUS episodes since diagnosis	Renal Transplant /dialysis ¹	PT Frequency/ Type	Hemat norm ² / Complete TMA resp ³ / TMA EF ⁴	Notes ⁵
198 - 001	38	CFHR1-CFHR3 mutation	0	Y/N	Once every 2 weeks - plasma exchange	Y/N/Y	TMA event free for 358 days. Creatinine levels remained elevated but stable.
198 002	27	None	0	Y/N	Once every 2 weeks - plasma exchange	N/N/Y	Hemoglobin and LDH maintained within normal range, except for a brief elevation of LDH. Platelet count and creatinine were stable but remained abnormal.
198 - 003	52	CD46 (MCP)	0	N/N	Once per week - plasma exchange	Y/Y/Y	TMA event-free status maintained for 294 days. Creatinine decreased 46% compared to baseline, but remained abnormal.
203 - 001	48	CFI	3	Y (X2)/N	Once every two weeks - FFP	Y/N/Y	No change in creatinine level.
205 - 001	43	CFH	0	N/N	Twice weekly - plasma exchange	Y/N/N	TMA event-free status not achieved due to decrease in platelet count by 25% from baseline (platelet counts remained above normal). No appreciable improvement in creatinine levels.

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 Soliris (eculizumab)

ID	Age (yrs)	CRF Mutation	No. of aHUS episodes since diagnosis	Renal Transplant /dialysis ¹	PT Frequency/ Type	Hemat norm ² / Complete TMA resp ³ / TMA EF ⁴	Notes
243 - 001	15	CFH	3	N/N	Once weekly - plasma exchange	Y/N/Y	Hematologic Normalization maintained from Day 56-until day 112, when LDH increased to 327. Patient did not continue into the extension period. Creatinine was stable, but remained high. Patient restarted eculizumab (without plasma therapy) using commercial supplies 11 weeks after the last dose of study drug when the subject experienced another aHUS exacerbation. Retreatment resulted in normalization of platelet count, LDH levels, and reduction in creatinine to baseline levels.
250 - 001	32	CFH	3	N/N	Twice weekly - FFP	Y/Y/Y	Creatinine levels decreased by 26% from day 70 until day 210 (140 days), then increased but remained below baseline level. <i>Reviewer comment: This "complete TMA response" does not appear to be clinically relevant.</i>
250 - 002	25	CFI	7	Y (X4)/N	Once weekly - plasmapheresis	N/N/Y	LDH, which increased approximately 50% during eculizumab therapy, became abnormal from day 7 to data cutoff. Platelet counts fluctuated between 92 X10 ⁹ /L and 164 X10 ⁹ /L. Creatinine remained stable but elevated. Remained on therapy at data cutoff (Day 309).
250 - 003	17	Factor B gain of function mutation	2	N/N	Once weekly FFP	Y/N/Y	Creatinine levels remained stable but elevated on eculizumab therapy. TMA event-free for 265 days.

- ¹ renal transplant prior to initiation of eculizumab or dialysis within 8 weeks prior to eculizumab therapy.
- ² Hematologic normalization was defined as normalization of platelet count and LDH defined by consecutive measurements which spanned at least four weeks.
- ³ Complete TMA response was defined as hematologic normalization plus improvement in renal function (at least a 25% reduction in serum creatinine by consecutive measurements spanning at least 4 weeks).
- ⁴ TMA Event-Free status was defined as absence for at least 12 weeks of [1] decrease in platelet count of > 25% compared to the pre-plasma therapy baseline; [2] plasma therapy while receiving eculizumab and [3] new dialysis requirement or need for increased frequency of dialysis.

Abbreviations: ID: patient ID number; yrs: years; CRF: Complement Regulatory Factor; No.: number; aHUS: atypical hemolytic uremic syndrome; N; no; Y: yes; PT: Plasma Therapy; TMA: thrombotic microangiopathy; Hemat norm: hematologic normalization; Complete TMA resp: complete TMA response; TMA EF: TMA event-free; LDH: lactate dehydrogenase; FI: Complement Factor I; CFH: Complement Factor H; Anti-CFH ab: anti-complement factor H antibody; MCP: membrane cofactor protein; eGFR: estimated glomerular filtration rate;

6.4 Study C09-001r Retrospective Study of Patients with aHUS

6.4.1 Study C09-001r Patient Demographics

Table 22, Table 23, and Table 24 show the baseline demographic and disease-related characteristics of subjects enrolled in Study C09-001r.

Table 22: Baseline Demographic Characteristics of Patients Enrolled in Study C09-001r

Patient Characteristics	Study C09-001r N = (30)
Age	
Median years of age (range)	12 (0.17; 51.4)
Adult, n (%)	11 (37)
Pediatric, n (%)	19 (63)
Infant (< 2 years)	5 (17)
Child (2 to < 12 years)	10 (33)
Adolescent (12 to < 18 years)	4 (13)
Gender (n, %)	
Female	16 (53)
Male	14 (47)
Race (n, %)	
White	23 (77)
Black	2 (7)
Other	5 (17)

Table 23: Summary of aHUS Disease History of Patients in Study C09-001r

Characteristic	Study C09-001r N = (30)
Time from aHUS diagnosis to first dose	
Median months (range)	10.9 (0.23, 176)
Prior renal transplant, n (%)	11 (37)
First aHUS exacerbation	12 (40)
At Least one known CRF mutation or auto-antibody, n (%)	14(47)
Multiple CRF mutations or auto-antibodies n, (%)	1 (3)
Type of CRF abnormality, n(%)	
Factor H mutation	9 (30)
Factor H mutation with another CRF mutation	1 (3)
C3 gain of function mutation	3 (10)
MCP Mutation	1 (3)

Abbreviation: CRF: Complement Regulatory Factor

Table 24: Key Characteristics of Current aHUS Exacerbation and Baseline Laboratory Parameters of Patients Enrolled in Study C09-001r

Characteristic	Study C09-001r N = (30)
<u>Current Exacerbation</u>	
Time from onset of current exacerbation to first dose	1.3 (0.1, 15.8)
Proportion of patients who received PT within 7 days of eculizumab, n (%)	21 (70)
No. PT sessions administered 28 days prior to the first dose, median (range)	8 (0, 29)
Proportion of patients requiring dialysis within 7 days of eculizumab, n (%)	8 (30)
Duration of exacerbation, n (%)	
2 months or less	20 (67)
more than 2 months	8 (26)
no current exacerbation	2 (7)
<u>Baseline Laboratory Parameters</u>	
Platelet Count (x 10 ⁹ /L), median (range)	159 (25, 381)
LDH (U/L), median (range)	453 (158, 1859)
Creatinine (µmol/L), median (range)	159 (15, 968)

Characteristic	Study C09-001r N = (30)
eGFR range (ml/min/1.73 m ²), n(%)	
<15 (Kidney failure)	8 (27)
15-29 (CKD4) (Severe)	5 (17)
30-59 (CKD3) (Moderate)	11 (37)
60 or higher	6 (20)

Abbreviation: PT: plasma therapy

Twenty-eight of the 30 patients enrolled had comparable disease profiles to patients enrolled in either Study C08-002 (PT resistant) or Study C08-003 (PT sensitive). Twelve patients received eculizumab for their presentation of aHUS. The duration of the current aHUS exacerbation was less than two months for 20 patients, and eight patients were being treated for an aHUS exacerbation that was ongoing for more than two months (more closely resembling the PT-sensitive patients enrolled in Study C08-003). Nine patients had abnormal platelet count and LDH prior to starting eculizumab. Eleven patients (37%) required dialysis prior to starting eculizumab; eight patients underwent dialysis at least once within a week of the first dose. A total of 24 (80%) patients received plasma therapy within 28 days of receiving eculizumab; 21 (70%) received plasma therapy within a week of the first dose.

Two patients did not exhibit clinical manifestations of aHUS at the time of eculizumab therapy; these patients were treated in an attempt to prevent aHUS-related complications following renal transplant (Patient 110-007) or in preparation for renal transplant (Patient 192-023).

All patients received concomitant therapy while being treated with eculizumab. The following types of concomitant medications were used by at least half of the patients enrolled in Study C09-001r (in descending order, by frequency):

- Vaccinations, including the meningococcal vaccine: (97%)
- Antianemic preparations (93%)
- Calcium channel blockers (93%)
- Systemic antibacterial agents (87%)
- Beta Blockers (80%)
- Drugs for acid-related disorders (77%)
- Diuretics (73%)
- Agents acting on the renin-angiotensin system (67%)
- Systemic corticosteroids (60%)
- Mineral supplements (53%)
- Analgesics (50%)
- Other Antihypertensives (50%)

The majority of patients received erythropoietin stimulating agents; Fifteen (50%) received darbepoetin alfa, 6 (20%) received epoetin alpha, 3 (10%) received epoetin beta, and 3 (10%) received an unspecified type of erythropoietin.

6.4.2 Subject Disposition in Study C09-001r

A total of 11 (37%) patients discontinued eculizumab treatment. Table 25 summarizes the reasons for discontinuation of eculizumab.

Table 25: Reasons for Treatment Discontinuation in Study C09-001r

Reason for Discontinuation	Number (%) of patients (N = 30)	Patient ID	Comments
Lack of efficacy	6 (20)	012-003, 120-008, 111-014, 191-021, 018-022, 020-026	
Death	2 (7)	192-023, 121-029	<i>Reviewer comment: Deaths do not appear to be related to eculizumab toxicity.</i>
Normalization of parameters of hematologic and renal function	1 (3)	210-006	
Patient Request	1 (3)	261-013	At the time of discontinuation, patient had normal hematologic parameters and improved renal function. According to the sponsor, patient indicated that she was discontinuing eculizumab because "renal function was nearly normalized." No aHUS exacerbation was reported 9 months after discontinuing eculizumab.
Administrative decision	1 (3)	211-015	This patient had stable hematologic and renal function parameters (on chronic dialysis) off plasma therapy for 40 days prior to starting eculizumab. Discontinued eculizumab after 169 days of therapy. Reviewer comment: Continued dialysis requirement with stable hematologic parameters during eculizumab therapy. Discontinuation does not appear to have been related to an adverse event.

6.4.3 Analysis of Key Endpoint(s) in Study C09-001r

Of the 30 patients enrolled in Study C09-001r, 11 patients (37%) required dialysis for renal failure prior to receiving eculizumab. As indicated in Table 26, 4 of the 11 patients (36%) who required dialysis prior to starting eculizumab treatment discontinued dialysis after eculizumab was initiated:

Table 26: Patients who discontinued dialysis after initiation of eculizumab in Study C09-001r

Patient ID	Age (years)	Dialysis Start Day	Dialysis End Day	Dialysis Frequency	Approximate duration of PT prior to receiving eculizumab
033-001	6	-19	-5	Once daily	1 month
013-005	0.5	-32	0	Three times per week	1.5 months
014-009	16	-2	-2	Once	18 days
044-012	10	0	0	Once	2 days

Reviewer comment: All of the patients who discontinued dialysis during this study were pediatric. These pediatric patients appear to resemble the "plasma therapy-resistant population" enrolled in Study C08-002, because the duration of PT and dialysis prior to starting eculizumab was relatively short.

Two adult patients (7%) developed a new dialysis requirement during eculizumab treatment:

- Patient 012-003 developed a dialysis requirement on day 14; eculizumab treatment was discontinued after the fourth dose due to a lack of treatment response.
Reviewer Comment: This 51-year old patient also had dermatomyositis, no identified complement regulatory factor mutation, and unknown ADAMTS-13 activity level.
- Patient 213-028 was a 31 year old man who developed a second exacerbation of aHUS on Day 17 of eculizumab therapy, triggered by fever. He underwent dialysis on Days 18 and 19, and again on a thrice weekly basis for approximately from day 48 until Day 119. Renal function subsequently improved, and the patient discontinued dialysis. On Day 248, he remained dialysis-free on eculizumab therapy. *Reviewer comment: this patient did not receive the dose of eculizumab that is proposed for this indication. He received 600 mg on Day 0 and Day 14, instead of 900 mg.*

A total of 19 pediatric patients (ages 2 months to 17 years) received Soliris in aHUS Study 3. 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 17 years of age (n= 4).

Table 27 summarizes key efficacy results for adult and pediatric patients enrolled in Study C09-001r.

Table 27: Efficacy Results in all Patients Enrolled in Study C09-001r

Efficacy Parameter	Pediatric Patients n=19	Adult Patients n=11	All Patients N=30
Hematologic Normalization	8/19 (42)	2 (18)	10 (33)
Complete TMA response, n (%)	8/19 (42)	2 (18)	10 (33)
Daily TMA intervention rate, median (range)			
Before eculizumab	0.31 (0, 2.38)	0.38 (0, 1.13)	0.34 (0, 2.4)
On eculizumab treatment	0 (0, 0.08)	0(0, 0.41)	0 (0, 0.41)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m ² in all treated patients, n (%)	9/19 (47)	2 (18)	11 (37)
After adjustment ¹	7/19 (37)	2(18)	9 (24)
eGFR improvement (mL/min/1.73 m ²), median (range)	41 (21,93)	57 (38,75)	41 (21,93)
Duration of improvement (days), median (range)	178 (43, 357)	71 (71, 118)	119 (43, 357)

¹. Deducted two patients because one patient received dialysis throughout the study period and another patient received eculizumab as prophylaxis following renal allograft transplantation.

Of the 11 patients who had improvement of eGFR by at least 15 ml/min/1.73 m² for a minimum of four weeks, two cases are not clinically relevant. Patient 016-016 remained on dialysis during the study period, and Patient 110-007 received eculizumab as prophylaxis following renal allograft transplantation.

Twenty patients remained free of a new dialysis requirement or need for plasma therapy, for a minimum of 12 weeks. Of the patients who were TMA event-free, the median duration of event-free status was 214 days. (min 123 days, max 646 days).

6.4.4 Analysis of supportive efficacy data for Study C09-001r

The applicant provided analyses of changes in laboratory markers of hemolysis and microangiopathy to provide supportive evidence that eculizumab decreases thrombotic microangiopathy in patients with aHUS.

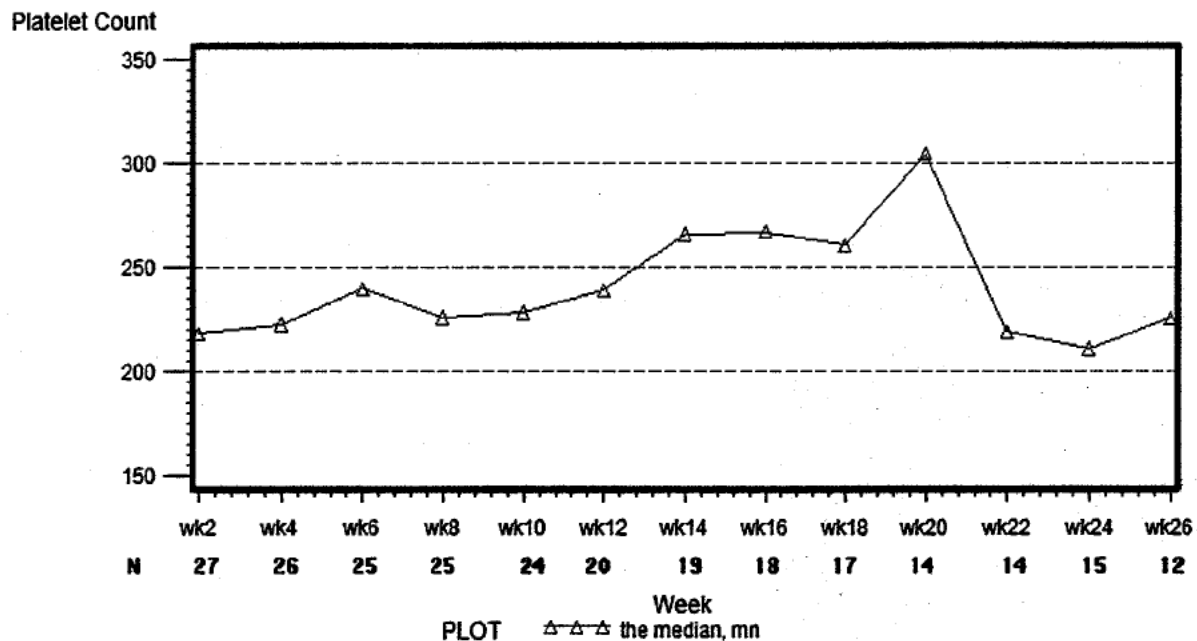
Reviewer note: analysis of haptoglobin levels does not provide meaningful information because this parameter was not consistently measured in this retrospective study.

Platelet Count Change from Baseline

The median platelet count at baseline for subjects enrolled in Study C09-001r was $159 \times 10^9/L$ (range: (25, 381)). Thirteen of 30 patients (43%) had a platelet count below 150×10^9 at baseline. Figure 13 provides a graphic representation of the median platelet count ($\times 10^9/L$) starting at Week 2 of eculizumab therapy. This figure illustrates that the median platelet count rose by Week two of therapy, and that this rise was generally sustained throughout the 26 week treatment period.

Figure 13: Median Platelet Counts in Study C09-001r

Median Platelet Count (C09-001R)

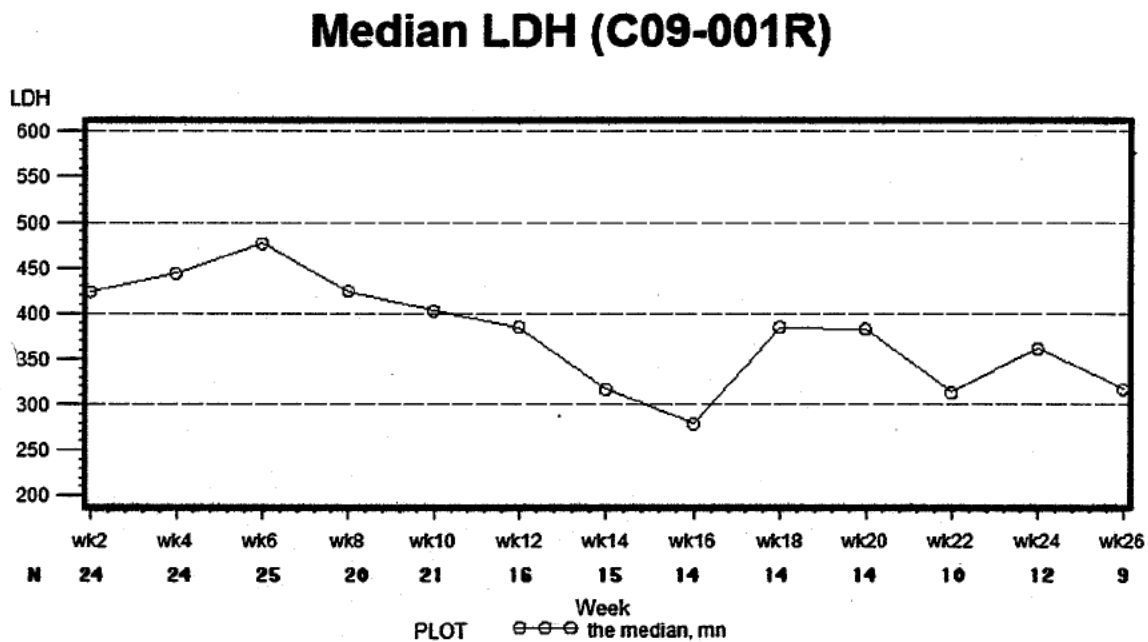


Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

Change in LDH levels from baseline

The median lactate dehydrogenase (LDH) level at baseline for subjects enrolled in Study C09-001r was 453 (158, 1859). Ten patients (59%) had an elevated LDH at the time of the diagnosis of the current aHUS episode. The median LDH at baseline for subjects enrolled in Study C08-002 was 269 U/L (134, 634). Twenty of 30 (67%) patients had an LDH level above the upper limit of normal at baseline. Eighteen of 30 (60%) patients exhibited LDH levels at or below the upper limit of normal for at least 4 weeks during the study period. Figure 14 provides a graphic representation of the median LDH (in U/L) starting at Week 2 of eculizumab therapy. This figure illustrates that the median LDH consistently remained at or below baseline levels after Week 8.

Figure 14: Median Serum LDH Levels in Study C09-001r



Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

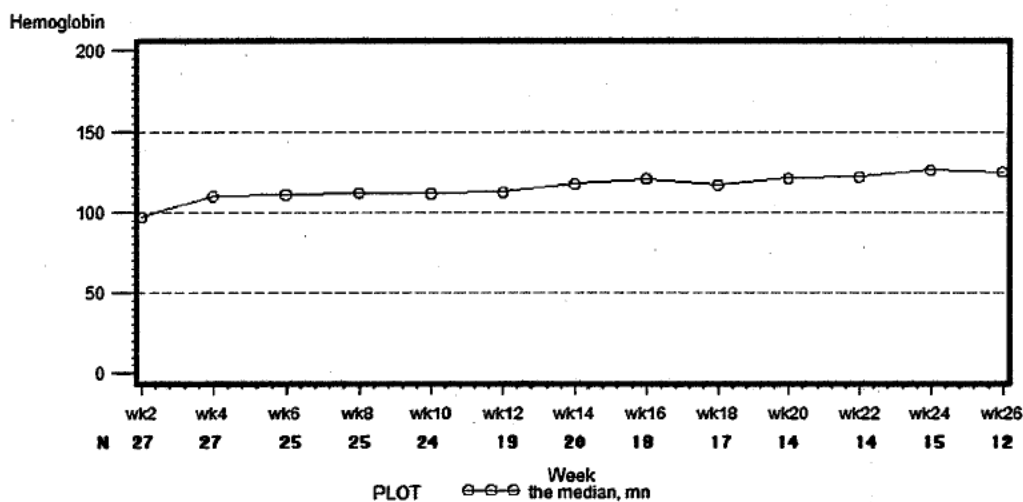
Change in Hemoglobin from Baseline

In Study C09-001r, 13 of 30 patients (43%) exhibited an increase in hemoglobin by at least 2 g/L that lasted a minimum of 4 weeks after starting eculizumab therapy. Figure 15 provides a graphic representation of the median hemoglobin level (in g/L) starting at Week 2 of eculizumab therapy.

It is difficult to assess the contribution of eculizumab in the improvement of anemia due to confounding factors. The majority of patients were treated with erythropoietin stimulating agents prior to and during the study. Additionally, seven patients required transfusion of blood products (primarily PRBCs) prior to receiving eculizumab, and six patients required transfusion of blood products (primarily PRBCs) during the study period after receiving eculizumab.

Figure 15: Median Hemoglobin Levels in Study 009-001r

Median Hemoglobin Level (C09-001R)



Source: FDA analysis of data provided by Alexion (provided by Kyung Lee, Office of Biostatistics)

6.4.5 Narrative Summaries for Patients Enrolled in C09-001r

Table 28 provides a brief summary of key characteristics and outcomes for patients enrolled in Study C09-001r. Entries for patients who discontinued dialysis during the eculizumab treatment period are shaded in gray.

Clinical Review
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 Soliris (eculizumab)

Table 28: Patient Summaries for Study C09-001r.

ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant / dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
033-001	6	None	4	N/Y	Y/Y/Y	Prior to eculizumab, received daily plasma exchange, hemodialysis, IVIG, immunosuppressants and antibiotics without improvement in hemolysis, thrombocytopenia or renal function. As of Nov 2009, the date of IC, patient continued dialysis free and continued eculizumab treatment. <i>Note: had a breakthrough aHUS episode triggered by S. pneumoniae pneumonia 206 days after starting eculizumab; this episode resolved 6 days later.</i>
011-002	21	CFH	0	N/N	Y/N/Y*	Had anaphylaxis secondary to plasma therapy prior to initiating eculizumab. Prior to this had received daily plasmapheresis, immunosuppressants, corticosteroids, rituximab. Platelet count normalized but LDH and renal function remained abnormal prior to eculizumab. After eculizumab, LDH normalized, renal function remained abnormal. Patient remained on eculizumab as of data cut-off.

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant / dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event-free ⁴	Notes
012-003	51	None	0	N/N	N/N/N	Newly diagnosed aHUS in the setting of dermatomyositis. Received plasma infusion or exchange daily, but experienced new thrombocytopenia, hemolysis prior to eculizumab. Dialysis initiated 14 days after starting eculizumab. Eculizumab discontinued after the fourth dose due to lack of efficacy.
022-004	1.6	None	4	N/N	Y/Y/Y	Diagnosed with aHUS at 7 days of age. Received daily plasma therapy, steroids, anticoagulants, thrombolytics for approximately one month prior to receiving eculizumab. Just prior to starting eculizumab creatinine was 265 µmol/L (normal: 18-35 µmol/L), platelet count was 25 X 10 ⁹ /L, and LDH was 1859 U/L. Received plasma therapy on Study Days 1-5, and underwent dialysis once on Study Day 2. Creatinine normalized nine weeks after starting eculizumab. Sustained improvement in renal function for 460 days. Had one brief aHUS exacerbation on therapy, but remained on eculizumab at the time of data cut-off.

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant / dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
013-005	5	None	0	N/Y	Y/Y/Y	Received intensive plasma therapy for approximately 1.5 months prior to eculizumab, and hemodialysis three times per week for approximately one month prior to eculizumab. Off dialysis after starting eculizumab. Remained on eculizumab at data cut-off (on Day 128 of therapy). <i>Reviewer comment: it is unclear whether this patient had typical (diarrhea associated HUS) or aHUS. This initial aHUS episode was triggered by a febrile gastrointestinal illness, but data regarding presence of shiga-toxin is not included in the CSR. Additionally, no complement regulatory factor mutations were identified, which would have confirmed an aHUS diagnosis. ADAMTS-13 activity was 113%.</i>
210-006	2	CF3 gain of function	0	N/N	Y/Y/Y	Received plasma therapy prior to eculizumab, without improvement in renal function or thrombocytopenia. Starting on Day 14 of eculizumab therapy, achieved sustained improvement in eGFR from 32 ml.min/1.73 m ² (baseline) to between 61 and 80 ml/min/1.73 m ² . Discontinued eculizumab on 2/1/2010 after 134 days of therapy due to sustained normalization of hematologic and renal parameters.

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant / dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
110-007	10	Factor H	7	Y/N	N/N/Y	Ecuzumab administered as prophylaxis for aHUS 11 days following renal transplant. Patient had normal hematologic and renal function parameters prior to initiation of ecuzumab. Remained on ecuzumab at data cut-off (Day 446 of therapy), with sustained normal renal function.
120-008	15	None	0	N/Y	N/N/N	Had normal hematologic parameters while on plasma therapy, but required dialysis on a regular basis starting 96 days prior to starting ecuzumab. Ecuzumab discontinued after two doses due to lack of improvement in renal function. Pt remained on dialysis.
014-009	16	CF3 gain of function	3	Y (X3)/Y	Y/Y/Y	Received daily plasmapheresis for approximately 2 weeks and one dialysis treatment prior to ecuzumab. Plasma therapy was discontinued within one week of starting ecuzumab. GFR improved by 29 ml/min/1.73 m ² for 43 days. Patient remained on ecuzumab for 130 days, and was continuing ecuzumab at data cut-off.
015-010	5	None	13	N/N	N/N/Y	Treated with plasma exchange, antibiotics and antihypertensives, with normalization of platelet count, hemoglobin and creatinine levels prior to ecuzumab. Had two serious adverse events during ecuzumab treatment: fever and line infection. Continued ecuzumab at data cut-off.
260-011	8	CFH	3	N/N	N/N/Y	Required plasma therapy prior to ecuzumab. No change in renal function on ecuzumab. Remained on ecuzumab at data cut-off.

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant / dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
044-012	10	None	1	YY	YYY	Developed acute allograft failure, requiring plasmapheresis and dialysis for two days prior to eculizumab. Starting Day 14 of eculizumab therapy, eGFR improved at least 15 ml/min/1.73 m ² from baseline (13 ml/min/1.73 m ²). The improvement was sustained for 178 days (range: 40 – 110 ml/min/1.73 m ²). Patient remained on eculizumab at data cut-off.
261-013	19	None	0	N/N	YYY	Required plasma therapy, corticosteroids, and immunosuppressants prior to eculizumab. Permanently discontinued plasma therapy after starting eculizumab. Exhibited a sustained (118 days) improvement in eGFR from baseline (23 ml/min/1.73 m ²) (range: 42-74 ml/min/1.73 m ² after eculizumab). Discontinued eculizumab after 161 days of treatment, with no exacerbation 9 months after discontinuation. <i>Reviewer comment: this initial aHUS episode was triggered by gastroenteritis. It is unclear whether this episode is consistent with aHUS rather than typical diarrhea-associated HUS.</i>
111-014	18	None	2	N/N	N/N/N	Treated with plasma exchange without improvement in renal or hematologic parameters prior to eculizumab. Patient received single dose of eculizumab with transient improvement in renal and hematologic function. Experienced exacerbation 33 days later. Eculizumab resumed for three more doses, but discontinued due to lack of improvement in renal function. ESRD followed.

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant / dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event-free ⁴	Notes
211-015	44	MCP mutation	0	N/Y	N/N/Y	This patient required chronic dialysis starting three months prior to starting eculizumab. Plasma therapy was discontinued approximately 40 days prior to starting eculizumab, and platelet count remained normal at the time of initiation of eculizumab. The patient remained on dialysis during eculizumab therapy. Eculizumab therapy discontinued after 169 days on therapy due to "administrative decision" . <i>Reviewer comment: the sponsor considers this patient TMA "event-free" because there was no increase in dialysis requirement during eculizumab therapy. However, in this case, TMA event free status is not clinically relevant because the patient didn't require plasma therapy prior to starting eculizumab.</i>

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant / dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
016-016	3	None	0	N/Y	N/N/Y	This patient initially presented with new onset seizures and was placed on corticosteroids and antiepileptics. Hemolytic anemia, thrombocytopenia, and renal failure developed two weeks later. There were multiple comorbid conditions requiring hospitalization in the pediatric intensive care unit, including deep venous thrombosis in the right shoulder, pulmonary hemorrhage, multiple infections, and avascular necrosis, prior to eculizumab therapy. This patient remained on dialysis, intermittent plasma therapy, and intravenous immunoglobulin therapy during the eculizumab treatment period. Experienced disseminated fungal infection on day 20 of treatment. Pt remained on eculizumab, requiring dialysis, ventilator, g-tube feedings at data cutoff (Day 205). <i>Reviewer comment: The sponsor indicated that this patient had a transient improvement in eGFR, which is also not clinically relevant because the patient continued to require dialysis daily.</i>
212-017	1	CFH mutation	1	N/N	N/N/N	Two separate eculizumab therapy periods. She received a single dose of eculizumab, then resumed eculizumab therapy two months later. Experienced aHUS exacerbation on day 185 of eculizumab therapy. Remains on eculizumab and off plasma therapy at data-cut off (Day 279).

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
190-018	42	CF3 gain of function	3	Y (X2)/N	N/N/Y	Plasma exchange therapy three times per week prior to initiation of eculizumab. Had three aHUS exacerbations during eculizumab treatment, but was TMA event free per the investigator. Free of plasma therapy and dialysis, remaining on eculizumab therapy at data cutoff.
017-019	6	Missense mutation of CFH	2	Y (X1)/N	Y/N/Y**	Normal platelet count and renal parameters on plasma therapy. Maintained normal renal function and hematologic parameters on eculizumab therapy without need for plasma therapy.
251-020	17	CFH	3	Y (X3)/N	N/N/Y	Exacerbation initially treated with biweekly plasmapheresis for 6 months with stable hematologic and renal function. Plasma therapy discontinued within 2 weeks of eculizumab therapy. Remained on eculizumab at data cut-off.
191-021	1.2	None	1	N/N	N/N/N	Initial presentation of hemolysis and renal failure with rotavirus diarrhea. Diagnosed with aHUS at first exacerbation. Platelets normalized with plasma therapy. Patient discontinued eculizumab after 32 days when aHUS exacerbation occurred triggered by Influenza A, requiring plasma therapy.
018-022	31	None	1	Y (X1)/Y	N/N/N	Treated with plasmapheresis, immunosuppressants, anti-hypertensive agents, hemodialysis until developed allergic reaction to plasmapheresis. Received a single dose of eculizumab. Discontinued because no improvement in renal function occurred after this dose.

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant / dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
192-023	13	CFH, CFI, MCP, CFB gain of function	8	Y (X1)/Y	N/N/N	Received kidney transplant at 19 months of age, and underwent transplantectomy approximately five years later. Between eight and ten years of age, developed transient ischemic attacks secondary to severe carotid artery stenosis and transient facial paralysis. Eculizumab initiated prophylactically prior to scheduled kidney transplantation. Two days after last eculizumab treatment (Day 70), she underwent angioplasty for severe right carotid artery stenosis, suffered a stroke during surgery and died. <i>Reviewer comment: this severe adverse event was not related to eculizumab treatment.</i>
060-024	5	CFH	12	N/N	Y/Y/Y	Remained off plasma therapy and continued eculizumab at data cut-off. Starting on day 42 of eculizumab therapy, eGFR showed an improvement of 26 ml.min/1.73 m ² from baseline (54 ml.min/1.73 m ²). The improvement was sustained for 179 days (range: 72-95 ml/min/1.73 m ²).
019-025	4	CFH	0	N/N	Y/Y/Y	Sibling also had aHUS (died following combined liver/kidney transplant). Remained on eculizumab at data cut-off (Day 392 of therapy). Starting on Day 7, eGFR improved by at least 15 mL/Min/1.73 m ² from baseline (70 mL/min/1.73 m ²). eGFR improvement was sustained for 385 days (range; 121-174 ml/min/1.73 m ²).

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant / dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
020-026	0.1	None	0	N/Y	N/N/N	Transient improvement in hematologic parameters, continued requirement for FFP infusions and dialysis during eculizumab therapy. Discontinued eculizumab after 2 months due to continued renal function deterioration. Developed aHUS exacerbation associated with central line infection 5 days following discontinuation.
193-027	29	None	0	Y (X2)/N	N/N/Y	This patient had chronic renal failure, thrombosis, and hypertension since 1997. Received plasma exchange twice prior to initiation of eculizumab. Platelet count was normal prior to starting eculizumab therapy. This patient developed an aHUS exacerbation triggered by a febrile illness 24 days after the last eculizumab dose, but the outcome of this episode is unknown because it occurred six days prior to the date of data-cut-off. <i>Reviewer comment: this aHUS exacerbation may have occurred, in part because the patient missed a dose of eculizumab.</i>

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant / dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
213-028	31	CFH	2	Y/N	N/N/Y	Had new aHUS exacerbation associated with an infection on Day 16 of eculizumab therapy, requiring plasmapheresis and new dialysis. Eculizumab was restarted after resolution of the aHUS exacerbation. The patient remained on eculizumab therapy at data cut-off, off dialysis but without substantial improvement in renal function. <i>Reviewer comment. considered TMA event-free by Sponsor by strict definition – was off dialysis and plasma therapy with maintenance of platelet count from study day 119 until data cut off at study day 247 (127 days).</i>
121-029	47	None	0	N/Y	N/N/N	Patient with Non-Hodgkin's Lymphoma s/p developed GVHD and transplant-associated HUS. Developed aHUS exacerbation 7 weeks after starting eculizumab therapy associated with infection. Died on Study Day 88 of multi-system organ failure due to GVHD and pulmonary aspergillosis. <i>Reviewer comment: GVHD is a known risk factor for pulmonary aspergillosis. It is unknown whether eculizumab therapy increases the risk of invasive fungal infections, but it is not likely to have been a major risk factor, in this reviewer's opinion.</i>

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ID	Age (years)	CRF mutation	Number of aHUS episodes since diagnosis	Renal Transplant / dialysis ¹	Hematologic Normalization ² / Complete TMA response ³ / TMA event free ⁴	Notes
213-030	22	None	1	Y/Y	Y/Y/Y	Three eculizumab treatment sessions occurred over a 461-day period. When the first AHUS exacerbation occurred, this patient initially underwent plasma exchange, and then received a single dose of eculizumab. After this single dose of eculizumab, plasma therapy was discontinued and eGFR improved for 71 days (baseline: 33 ml/min/1.73m ² , compared to a range of 53-114 ml/min/1.73 m ² after eculizumab). One year later, the patient developed an aHUS exacerbation with acute renal allograft failure, and eculizumab treatment recommenced and continued for approximately two months. Renal function improved and platelet count normalized following eculizumab therapy. The patient missed her scheduled eculizumab infusion and developed another aHUS exacerbation approximately 1.5 months later. She was retreated with eculizumab two days prior to data cut-off, but the outcome of this treatment is unknown. <i>Reviewer comment: it is unclear whether a single dose of eculizumab is responsible for the improvement in renal function during the first treatment period, because creatinine was trending down prior to initiation of eculizumab.</i>

* This patient achieved hematologic normalization, but was not listed as achieving hematologic normalization in efficacy dataset submitted by sponsor.

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** This patient achieved hematologic normalization and TMA event-free status, but was not listed as achieving hematologic normalization or TMA event-free status in the dataset submitted by the sponsor.

- ¹ Renal transplant prior to initiation of eculizumab or dialysis within 8 weeks prior to eculizumab therapy.
- ² Hematologic normalization was defined as normalization of platelet count and LDH defined by consecutive measurements which spanned at least four weeks.
- ³ Complete TMA response was defined as hematologic normalization plus improvement in renal function (at least a 25% reduction in serum creatinine by consecutive measurements spanning at least 4 weeks).
- ⁴ TMA Event-Free status was defined as absence for at least 12 weeks of [1] decrease in platelet count of > 25% compared to the pre-plasma therapy baseline; [2] plasma therapy while receiving eculizumab and [3] new dialysis requirement or need for increased frequency of dialysis.

Abbreviations: ID: patient ID number; CRF: Complement Regulatory Factor; aHUS: atypical hemolytic uremic syndrome; N; no; Y: yes; TMA: thrombotic microangiopathy; LDH: lactate dehydrogenase; FI: Complement Factor I; CFH: Complement Factor H; MCP: membrane cofactor protein; CFB: complement factor B; CF3: Complement factor 3; eGFR: estimated glomerular filtration rate;

6.5 Subpopulations

Meaningful comparisons of eculizumab efficacy in different patient subpopulations are hindered by the small numbers of patients enrolled in Studies C08-002, C08-003, and C09-001r. All of the subgroup analyses presented below should be interpreted with caution due to the small numbers of patients enrolled in the registration studies submitted to this sBLA.

Patient Age

Table 29 summarizes the efficacy results for pediatric patients by age subgroup for all pediatric patients enrolled in the three studies submitted in this supplemental application. As Table 29 illustrates, there do not appear to be consistent differences in efficacy of eculizumab in the treatment of aHUS in adult and pediatric patients. Similarly, there do not appear to be consistent differences in the proportion of patients exhibiting hematologic normalization, complete TMA response, TMA event-free status, and sustained eGFR improvement within each pediatric age group.

Table 29: Comparison of Efficacy Results in Adult and Pediatric Patients Enrolled in Studies C08-002, C08-003, and C09-001r.

Efficacy Parameter n (%)	Pediatric Patients enrolled in all studies (years of age)			Adult Patients		
	<2 n = 5	2 - < 12 n = 10	12 to < 18 n = 10	Study C08- 002 n = 16	Study C08- 003 n = 15	Study C09- 001r n = 11
Hematologic Normalization	2 (40)	5 (50)	7 (70)	12 (75)	13 (87)	2 (18)
Complete TMA Response	2 (40)	5 (50)	2 (20)	10 (63)	5 (33)	2 (18)
TMA Event Free	2 (40)	9 (90)	8 (80)	14 (88)	11 (73)	7 (64)
Sustained eGFR improvement of at least 15 ml/min/1.73 m ² for a minimum of four weeks ¹	2 (40)	6 (60)	2 (20)	8 (50)	2 (13)	2 (18)

¹: during the treatment or extension study period

In the three aHUS studies combined, only one patient was 65 years of age or older. Therefore, subgroup analyses of efficacy in patients $\geq$ 65 years of age were not performed.

Race

Subgroup analyses based on race were not performed. Due to the small sample size, as well as the fact that over eighty percent of patients enrolled in the three registration studies (55 of 67 patients) are Caucasian, comparisons of efficacy by racial subgroup would not be meaningful. Therefore, this subgroup analysis was not performed.

Gender

Table 30 presents the results of FDA analysis comparing efficacy results for females with males. Based on this analysis, the effectiveness of eculizumab appears to be similar in males and females.

Table 30: Comparison of Efficacy Results by Gender

Efficacy Parameter n (%)	Studies C08-002, C08-003, C09-001r N = 67	
	Females n = 40	Males n = 27
Hematologic Normalization	25 (63)	16 (59)
Complete TMA Response	15 (38)	11 (41)
TMA Event Free	31 (78)	20 (74)
Sustained eGFR improvement of at least 15 ml/min/1.73 m ² for a minimum of four weeks ¹	11 (28)	11 (41)

Complement Regulatory Factor Mutation Status

The applicant also conducted subgroup analyses to compare the efficacy of eculizumab in patients with and without identified complement regulatory factor (CRF) mutations or auto-antibodies. Table 31 provides a comparison of key efficacy results by CRF mutation status in the prospective aHUS studies. These subgroup analyses indicate that the efficacy results for patients with and without identified CRF mutations or auto-antibodies appear to be comparable.

Table 31: Comparison of Efficacy Results by CRF Mutation Status in the Prospective aHUS Studies. (source: applicant conducted analyses)

Efficacy Parameter ¹	Study C08-002 N = 17		Study C08-003 N = 20	
	Identified CRF mutation or auto-antibody		Identified CRF mutation or auto-antibody	
	+	-	+	-
	(n = 13)	(n = 4)	(n = 14)	(n = 6)
Hematologic Normalization, n (%)	10 (77)	3 (75)	13 (93)	5 (83)
Maximum duration, days (range)	263 (175, 431)	237(196, 285)	294 (181, 336)	203 (154, 363)
Complete TMA Response, n (%)	9 (69)	2 (50)	3 (21)	2 (33)
Maximum duration, days (range)	267 (175, 389)	261 (237, 285)	224 (140, 238)	175 (83, 266)
eGFR improvement ² ≥ 15 ml/min/1.73 m ²	7 (54)	2 (50)	1 (7)	1 (17)

¹, from baseline through data cut-off

², measured in two consecutive measurements spanning at least 4 weeks.

In the retrospective study (C09-001r), 5/14 (36%) patients with an identified CRF mutation or auto-antibody exhibited an improvement in eGFR of at least 15 mL/min/1.73 m² for a minimum of four weeks, compared to 6/16 (38%) patients without an identified CRF mutation or auto-antibody.

6.6 Analysis of Clinical Information Relevant to Dosing Recommendations

Please refer to the clinical pharmacology review of this supplemental BLA for a discussion of efficacy based upon exposure. The sponsor performed exposure-response analyses for efficacy endpoints including TMA event-free status, change in renal function, and hematologic normalization. These analyses showed that the proportion of patients who achieved TMA event-free status, hematologic normalization, or a GFR improvement of at least 15 mL/min was not influenced by eculizumab exposure, body weight, or patient age. The clinical pharmacology reviewer concluded that this finding suggested that the selected doses provide sufficient exposure in patients of varying age and size.

6.7 Discussion of Persistence of Efficacy and/or Tolerance Effects

The minimum follow-up period for patients enrolled in the prospective studies (C08-002 and C08-003) was 26 weeks. At the time of data cut-off the median duration of eculizumab exposure was 38 weeks (range: 2 to 64 weeks) for Study C08-002 and 40 weeks (range: 26 to 52 weeks) for Study C08-003.

For these prospective studies, the sponsor analyzed the efficacy of eculizumab during the initial treatment period (from baseline to 26 weeks) and over the entire study period (from baseline through the data cut-off date). In Studies C08-002 and C08-003, the proportion of patients achieving hematologic normalization and Complete TMA response through the end of the 26 week treatment period and through the time of data cut-off were identical. Additionally, the TMA intervention rates calculated from baseline to 26 weeks were identical to the TMA intervention rates calculated from baseline to the respective data cut-off dates for both studies; this indicates that patients required a similar number of plasma therapy interventions and new or increased requirement for dialyses during the extension and treatment periods.

In Study C08-002, among the responders, the median maximum duration of Complete TMA response was 267 days (range 175 to 389 days). All patients who had achieved a complete TMA response continued to maintain this response at the time of data cut-off. In study C08-003, the median maximum duration of Complete TMA Response was 224 days (range: 83 to 226 days), and all patients who had achieved a Complete TMA response to eculizumab treatment continued to maintain this response as of the data cut-off date.

At the time of data cut-off in Studies C08-002 and C08-003, no patient experienced an aHUS exacerbation while being treated with eculizumab.

In Study C09-001r, four patients experienced TMA complications due an aHUS exacerbation after discontinuing eculizumab. In these patients, aHUS exacerbations occurred approximately 30 to 350 days following receipt of a single dose of eculizumab dose (patients 018-002, 212-017, 111-014, and 213-030); three of these patients subsequently restarted eculizumab treatment, and two remained on eculizumab at the time of data cut-off. *Reviewer note: these cases illustrate the potential for multiple episodes of thrombotic microangiopathy in atypical aHUS, and that eculizumab may be effective if reinstated following its discontinuation.*

Two patients in Study C09-001r (020-026 and 191-021) experienced an aHUS exacerbation within one week of the last eculizumab dose. One patient experienced an aHUS exacerbation associated with a central line infection on Day 71 of therapy, five days after receiving her last eculizumab dose. An additional patient developed an aHUS exacerbation associated with Influenza A infection on Day 32 of the study, four days after receipt of eculizumab. In both cases, eculizumab was discontinued.

Reviewer note: *These cases illustrate that some patients are vulnerable to aHUS exacerbations while being treated with eculizumab.*

Overall, the data from these studies demonstrate that eculizumab treatment resulted in improvement or stabilization of renal function and hematologic parameters in the absence of plasma therapy for up to one year in the majority of patients who were enrolled.

6.8 Additional Efficacy Issues/Analyses

Study C08-002 and C08-003 also examined changes in quality of life, as measured by the EuroQol 5D instrument, which uses a self-report questionnaire and a visual analog scale to assess 5 aspects of health-related quality of life and well-being: mobility, ability to independently care for self, ability to conduct usual activities, pain/discomfort, and anxiety/depression. Because results of quality of life assessments are not interpretable in single arm, unblinded trials, analyses of these data are not included in this clinical review.

7 REVIEW OF SAFETY

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety review focused primarily on the safety database compiled from the treatment of 67 patients with aHUS who were enrolled in Studies C08-002, C08-003, and C09-001r. In addition to conducting analyses of the safety data from these studies, summary data from the trials supporting the approval of eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria, the Soliris Annual Report covering the period of March 17, 2010 to March 16, 2011, and the Periodic Safety Update Report for the period of April 2, 2010 through April 1, 2011 were also reviewed.

7.1.2 Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 11.0 was used to code all adverse events. The adverse event database for Studies C08-001, C08-002, and C09-001r contained 238, 168, and 253 individual adverse event listings, respectively. However information about serious adverse events was not comprehensively collected during the retrospective data collection (as described in earlier sections, only adverse events of "special interest" were collected).

In Study C08-002 and C08-003, investigators rated adverse event severity using the following criteria:

- **Mild:** adverse events require minimal or no treatment and do not interfere with the **patient's daily activities**
- **Moderate:** adverse events that may cause some interference **with the patient's daily activities** and result in a low level of inconvenience or concerns with the therapeutic measures.
- **Severe:** adverse events that interrupt a **patient's usual daily activities and may** require systemic therapy. These events are usually incapacitating.

Review of adverse event datasets to determine whether if verbatim terms were appropriately coded using MedDRA preferred terms revealed no instances of inaccurate coding. In addition, based on review of a subset of Case Report Forms, the adverse event databases appear to be accurate and comprehensive.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The primary analysis of safety was performed on each of the three registration studies individually. In addition, pooled safety data from the prospective studies were analyzed to look for additional safety signals that were not evident when analyzing each study separately and to compare the incidence of adverse events among patients enrolled in each study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For a summary and discussion of demographic and disease-related characteristics for patients enrolled in Studies C08-002, C08-003, and C09-001r, please refer to Sections 6.2.1, 6.3.1, and 6.4.1, respectively.

Prospective aHUS Studies

Fifteen of 17 patients (88%) in Study C08-002 and all patients (N=20) enrolled in Study C08-003 completed the 26-week treatment period. The majority of patients elected to continue eculizumab treatment by entering the extension portion of the studies. The median duration of treatment was 38 weeks (range: 1-64 weeks) and 41 weeks (range 46-54 weeks) in Studies C08-002 and C08-003, respectively.

Dose reductions were not prespecified in the protocols for either study. In general, patients received the proposed dose and schedule of eculizumab, with only minor variations occurring in a small number of patients. Overall, 3/145 (2%) doses during the induction phase and 21/672 (3%) of maintenance doses were delayed. Two patients enrolled in Study C08-002 had a delay of more than 9 days during the induction phase of eculizumab therapy; in both cases, delay occurred due to a delay in delivery of drug. Seven patients in Study C08-002 and five patients in Study C08-003 had dosing delayed by more than 16 days (range: 17 days to 29 days) during the maintenance phase of treatment. For two patients, dosing was delayed due to serious adverse events; for the remainder, either the reason for the dose delay was not recorded, or it was delayed for logistical reasons.

Retrospective Study

The median eculizumab exposure for patients enrolled in Study C09-001r was 28 weeks (range: 1-94 weeks). Sixteen patients (53%) remained on eculizumab treatment for at least 26 weeks, and 20 of 30 patients (67%), remained on eculizumab at the time of data cut-off. Adult and adolescent patients weighing at least 40 kg received were treated using the same dosage regimen for eculizumab that was used in the prospective studies (C08-002 and C08-003). Alexion provided recommendations for pediatric dosing based on weight (identical to the proposed dosing regimen for patients less than 40 kg), to treating physicians of pediatric patients.

The actual dose administered to some patients in this retrospective study was different from dosing recommendations made by Alexion. In general, the maintenance dose administered to children who weighed less than 20 kg was than the weight-based dose proposed in this application. In addition, children weighing between 10 and 30 kg received doses during induction that were lower than the proposed dose for their weight. The FDA clinical pharmacology reviewer concluded that the deviations from the proposed dosing regimen did not result in clinically important differences in exposure.

Descriptive statistics of PK exposure parameters performed by the applicant indicated that the mean C_{min} values of eculizumab remained above 50 µg/mL during the induction and maintenance periods for all age groups, and that C_{max} values were less than 700 µg/mL during the induction and maintenance periods for all groups.

7.2.2 Explorations for Dose Response

The applicant did not conduct formal analyses of dose response. However, FDA analyses performed by Bahru Habtemariam, PharmD did not identify an exposure-response relationship for the efficacy endpoints of hematologic normalization, complete TMA response, or TMA event-free status. Similarly, the proportion of patients with TMA event free status, improvement in renal function, and hematologic normalization were

similar across different weight and age groups. Additional analyses did not show a relationship between eculizumab exposure and the development of hypertension or infection.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed to support this supplemental BLA. Neither genotoxicity nor long-term animal carcinogenicity studies of eculizumab have been conducted.

7.2.4 Routine Clinical Testing

7.2.5 Metabolic, Clearance, and Interaction Workup

No formal analyses to examine the effect of drug interactions on exposure or safety were conducted. All patients enrolled in Studies C08-002, C08-003, and C09-001r received other medications in addition to eculizumab. Please see Sections 6.2.1, 6.3.1, and 6.4.1 for details regarding the concomitant medications commonly used to treat patients enrolled in these studies.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are currently no pharmacologically related products other than other monoclonal antibodies used for the treatment of a variety of diseases. Hypersensitivity reactions, including infusion reactions, are typically associated with the use of monoclonal antibodies. The potential for development of neutralizing anti-human-antibodies is also a risk of therapy with monoclonal antibodies, such as eculizumab, that have human constant regions. The primary safety concern with Soliris is that its use confers increased risk for the development of meningococemia. Please see Section 2.4 for a discussion of the safety issues that have been identified in clinical studies and through analysis of postmarketing data of eculizumab accumulated since its approval in 2007.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in Studies C08-002 and C08-003. Two patients died in the retrospective study (C09-001r):

- One death occurred in a 13 year old girl (Patient 192-023) who received eculizumab in preparation for a kidney transplant. Five days after undergoing angioplasty (which was complicated by carotid artery dissection) for coronary artery stenosis, she developed a stroke and died on Day 80 of eculizumab therapy.

- Another death occurred in A 47 year old man (patient 121-029) with Non-Hodgkin Lymphoma status post hematopoietic stem cell transplantation complicated by **“uncontrolled” graft versus host disease** who received eculizumab for the treatment of his first aHUS episode following stem cell transplant. He died of multisystem organ failure due to worsening graft versus host disease and pulmonary aspergillosis on Day 88 of eculizumab therapy.

Comment: based on review of the narratives of these cases, it is unlikely that these patient deaths are related to eculizumab therapy.

7.3.2 Nonfatal Serious Adverse Events

Adverse events were designated Serious Adverse Events (SAEs) if they met one of the following criteria:

- resulted in death
- was immediately life-threatening (an event in which the subject was at risk of death at the time of the event)
- required inpatient hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability or incapacity
- was a congenital anomaly or birth defect

This definition of SAE is in accordance with ICH E6 Good Clinical Practice Guidelines. Serious adverse events were not comprehensively reported for the retrospective data collection in Study C09-001r. For Studies C08-002 and C08-003, SAEs, regardless of causality assessment, were collected during the study period through eight weeks after the last dose of eculizumab.

Prospective Studies (C08-002 and C08-003)

Twenty of 37 (54%) patients enrolled in the prospective studies experienced a serious adverse event. Fifteen patients (88%) in Study C08-002 and experienced at least one serious adverse event, and five patients (25%) in Study C08-003 experienced at least one serious adverse event.

In both studies, the most common serious adverse events were hypertension-related (6 events), infectious (5 events), and renal (5 events).

Table 32 summarizes the per-patient incidence of SAEs by System Organ Class (SOC) for the prospective studies, and Table 33 summarizes the per-patient incidence of SAEs by preferred term.

Table 32: Per Patient Incidence of Serious Adverse Events by MedDRA SOC for Prospective aHUS Studies

SOC	Study C08-002	Study C08-003	Both Studies
	N = 17	N = 20	N = 37
n (%)			
Vascular disorders	6 (35)	2 (10)	8 (22)
Infections and infestations	4 (24)	1 (5)	5 (14)
Renal and urinary disorders	4 (24)	1 (5)	5 (14)
Nervous system disorders	2 (12)	1 (5)	3 (8)
Blood and lymphatic system disorders	2 (12)	0 (0)	2 (5)
Cardiac disorders	2 (12)	0 (0)	2 (5)
Gastrointestinal disorders	1 (6)	1 (5)	2 (5)
Musculoskeletal and connective tissue disorders	2 (12)	0 (0)	2 (5)
General disorders and administration site conditions	1 (6)	0 (0)	1 (3)
Hepatobiliary disorders	1 (6)	0 (0)	1 (3)
Immune system disorders	0 (0)	1 (5)	1 (3)
Injury, poisoning and procedural complications	1 (6)	0 (0)	1 (3)
Respiratory, thoracic and mediastinal disorders	1 (6)	0 (0)	1 (3)
Surgical and medical procedures	0 (0)	1 (5)	1 (3)

Table 33: Per Patient Incidence of Serious Adverse Events by MedDRA Preferred Term for Prospective aHUS Studies

Preferred Term	Study C08-002 N = 17		Study C08-003 N = 20		Prospective Studies Combined N = 37	
	n	%	n	%	n	%
Renal Impairment	3	18	0	0	3	8
Upper Respiratory Tract Infection	2	12	0	0	2	5
Accelerated Hypertension	2	12	0	0	2	5
Hypertension	2	12	0	0	2	5
Malignant Hypertension	2	12	0	0	2	5
Leukopenia	1	6	0	0	1	3
Pancytopenia	1	6	0	0	1	3
Bradycardia	1	6	0	0	1	3
Pericardial Effusion	1	6	0	0	1	3
Esophagitis	1	6	0	0	1	3
Peritonitis	0	0	1	5	1	3
Pyrexia	1	6	0	0	1	3
Cholelithiasis	1	6	0	0	1	3
Transplant Rejection	0	0	1	5	1	3
Clostridium Difficile Colitis	0	0	1	5	1	3
Gastroenteritis	1	6	0	0	1	3
Varicella	1	6	0	0	1	3
Respiratory Fume Inhalation Disorder	1	6	0	0	1	3
Back Pain	1	6	0	0	1	3
Systemic Lupus Erythematosus	1	6	0	0	1	3
Convulsion	1	6	0	0	1	3
Headache	0	0	1	5	1	3
Reversible Posterior Leukoencephalopathy Syndrome	1	6	0	0	1	3
Hematuria	1	6	0	0	1	3
Renal Failure Chronic	0	0	1	5	1	3
Dyspnea	1	6	0	0	1	3
Catheter Removal	0	0	1	5	1	3
Hypotension	0	0	1	5	1	3
Vein Disorder	0	0	1	5	1	3

Vascular Disorders

The most commonly reported SAEs were related to the Vascular Disorders, which occurred in 8/37 (22%) of patients in the prospective studies. Within the vascular disorder SOC, the most common adverse events were hypertensive adverse events. Accelerated hypertension, hypertension, and malignant hypertension occurred in 2 patients each. Hypotension, occurred in one patient, and a vein disorder (venous sclerosis) occurred in another patient.

Comment: All hypertension SAEs occurred in patients with who had hypertension prior and renal impairment prior to enrolling in Study C008-002; none of these patients suffered a recurrence of hypertensive SAEs despite continuation of eculizumab; Therefore, it is unlikely that eculizumab played a major causal role in the development of these SAEs.

Infections and Infestations

Five patients (14%) experienced infectious SAEs. Within this SOC, two patients experienced upper respiratory tract infections, and varicella (in a patient on immunosuppressant therapy), gastroenteritis, and clostridium difficile colitis were reported in one patient each.

Renal and urinary disorders

Adverse events within the renal and urinary disorder SOC were reported in five patients. Three patients developed worsening renal impairment, one patient developed hematuria, and chronic renal failure was reported in another patient.

Comment: the Renal SAEs appear to be related to lack of efficacy of eculizumab in mitigating thrombotic microangiopathy-induced renal damage in these patients, instead of adverse events.

Nervous System Disorders

Three patients developed neurologic adverse events considered to be SAEs. Two SAEs, convulsion and reversible posterior leukoencephalopathy developed secondary to hypertension. In addition, another patient was hospitalized due to a severe headache during the eculizumab treatment period. All of the SAEs resolved.

Blood and Lymphatic Disorders

Transient leukopenia occurred in one patient without infectious sequelae. Worsening pancytopenia occurred in a patient who received concomitant immunosuppressive therapy for prophylaxis of rejection of a renal allograft.

Cardiac Disorders

Two cardiac SAEs were reported: Pericardial effusion (in a patient with preexisting cardiomyopathy) and bradycardia. Both SAEs were considered unrelated to eculizumab.

Gastrointestinal Disorders

Peritonitis occurred in a patient on chronic peritoneal dialysis enrolled in Study C08-003, and esophagitis occurred in a patient (with a prior history of esophagitis) enrolled in Study C08-002.

Musculoskeletal and Connective Tissue Disorders

Back pain occurred in one patient who had a history of intermittent back pain prior to initiating eculizumab therapy. and another patient was diagnosed with Systemic Lupus Erythematosus one week after receipt of the first dose of eculizumab. *Comment: the patient was discharged from the study shortly thereafter.*

SAEs in other SOCs:

The following SAEs occurred in one patient each:

- cholelithiasis
- dyspnea (secondary to fluid overload, in a patient with a history of shortness of breath prior to eculizumab)
- pyrexia (in a patient on concomitant immunosuppressive therapy without a documented infectious source)
- transplant rejection
- catheter removal
- respiratory fume inhalation.

Retrospective aHUS Study (C09-001r)

The retrospective study collected only those serious adverse events that were **considered to be "of special interest",** which included meningococcal infection, serious infections, death, serious hemolysis after drug discontinuation, pregnancies, serious infusion reactions, immunogenicity and malignancies. The following serious adverse **events of "special interest" occurred in 7 patients (23%)** enrolled during the retrospective study:

- *Central line Infection* and *fever* in a five year old patient (patient 015-010)
- *Fungal Infection, urinary tract infection, peritonitis, sepsis and respiratory tract infection* (patient 016-016). This 2 year old pediatric patient was ventilator-dependent, on chronic corticosteroids, hospitalized in the pediatric intensive care unit for two months prior to commencement of eculizumab therapy)
- *Gram negative bacteremia (Stenotrophomonas maltophilia)*. occurred in a 47 year old patient (Patient 121-029) with a port-a-cath who had received prior stem cell transplantation for Non-Hodgkin Lymphoma. After recovering from this infection, he

developed a fatal SAE of *pulmonary aspergillosis* and *multisystem organ failure* in the setting of *worsening GVHD*.

- *Streptococcal pneumonia* occurred in a 3 year old patient on Study Day 77 (patient 033-001).
- *Pulmonary infection* occurred in a 29 year old patient who received concomitant tacrolimus for prevention of graft rejection (patient 193-027).
- *Upper respiratory tract infection* occurred in 1 year old patient on study day 186. (patient 212-017).
- A 13 year old patient (patient 192-023) who had a longstanding history of vascular disease developed a thrombosis of the left subclavian artery 71 days after initiation of eculizumab treatment. Two days later, she developed occlusion of the carotid artery and subclavian artery, followed by a fatal stroke during surgery for diffuse vascular lesions in the right carotid artery.

All serious adverse events required hospitalization. With the exception of the fatal serious adverse events of multisystem organ failure, worsening GVHD, and pulmonary aspergillosis that occurred in patient 121-029, and the fatal carotid artery dissection and stroke that occurred in patient 192-023, the remainder of the serious adverse events of **"special interest" resolved, and patients remained on eculizumab.**

In addition, two patients had thrombotic events during the eculizumab treatment period. One patient (016-016) developed a non-occlusive right jugular venous thrombosis associated with a central line that was not considered serious.

7.3.3 Dropouts and/or Discontinuations

Study C08-002

At the time of data-cut off, 13 of the 17 enrolled patients (76%) patients had completed the 26 week treatment period and continued to receive eculizumab. Of the four patients who discontinued eculizumab, two patients (patients 2-141-001 and 2-198-001) completed 26 weeks of eculizumab therapy but opted not to enroll in the extension period. Both patients had achieved hematologic normalization and a complete TMA response to eculizumab treatment, which appeared to be sustained through the last day of follow up.

One patient (2-140-001) discontinued **eculizumab after the fourth dose due to "adverse events" of worsening renal function** and pancytopenia., This patient received immunosuppressive medications (everolimus, azathioprin, leflunomid, prednisone, and mycophenolate mofetil) during the study period. Another patient (2-043-001) withdrew from the study following receipt of a single dose of eculizumab after being diagnosed with systemic lupus erythematosus.

Study C08-003

No discontinuations occurred due to adverse events in Study C08-003. At the time of data cut-off, 19 of 20 (95%) patients had completed the 26 week treatment period and continued to receive eculizumab. Patient 3-243-001 completed the 26 maintenance treatment phase, but decided not to enroll into the extension study. Approximately eleven weeks after discontinuing eculizumab, she developed another aHUS exacerbation, manifested by hypertension, edema, elevated creatinine, thrombocytopenia, and anemia. After eculizumab therapy recommenced, hematologic parameters resolved and renal function returned to baseline.

Study C09-001r

A total of 11 (37%) patients discontinued eculizumab treatment. Of the 11 patients who discontinued therapy, two patients (192-023, 121-029) discontinued eculizumab due to fatal adverse events in which eculizumab did not appear to play a causal role. Brief summaries of the clinical courses and fatal adverse events are presented in Sections 6.4.5 and 7.3.1, respectively. The nine remaining patients discontinued eculizumab for reasons other than the development of adverse events. Please refer to Section 6.4.2 for details regarding the reasons for discontinuation of eculizumab therapy in Study C09-001r.

7.3.4 Significant Adverse Events

The ICH E3 guidance considers other potentially important abnormalities, such as severe adverse events that do not meet the definition of a serious adverse event, potentially significant. A discussion of severe adverse events is included in Section 7.4.1 of this review.

An analysis of parameters of hepatic function **was conducted to look for Hy's Law cases** and assess whether there were signs of significant liver toxicity due to eculizumab. In Study C08-002, no patients had clinically significant elevations in AST, ALT or bilirubin. In Study C08-003, no patient had elevation in bilirubin. Ten patients had elevations in AST or ALT, but all elevations were limited to Grade 1.

In the retrospective study, the following two patients had simultaneous, clinically relevant elevations in bilirubin and hepatic enzymes. However, these cases did not **meet the definition of Hy's Law cases because** they either occurred prior to initiation of eculizumab, or occurred in the setting of an illness that was likely to cause hepatotoxicity.

- Patient 121-029 had concomitant elevations in bilirubin (up to 7.9 X ULN), AST (up to 10.9 X ULN) and ALT (up to 13.1 X ULN). However, these elevations occurred in the setting of worsening graft versus host disease (GVHD) and multisystem organ failure due to pulmonary aspergillosis.

- Patient 016-016 had elevations in bilirubin (2.0 X ULN), ALT (6.8 X ULN), AST (8.1 X ULN). However, elevations in these parameters, were evident prior to initiation of eculizumab. Additionally, they occurred in the setting of concomitant therapy with antiepileptic drugs and multiple pre-existing comorbidities that required patient hospitalization in the pediatric critical care unit prior to and during eculizumab therapy.

In addition, patient 251-020 had an ALT elevation without elevation in AST or bilirubin on Days 371 through Day 413 of therapy. This patient remained on eculizumab, with subsequent normalization of ALT.

7.3.5 Submission Specific Primary Safety Concerns

The primary safety concern with eculizumab is the increased risk of serious infections due to *Neisseria meningitidis*. This risk was identified prior to the initial approval of eculizumab for the treatment of patients with PNH, and a REMS is currently in place to mitigate the risk and morbidity associated with *N. Meningitidis* infections. In accordance with the REMS, all patients were either received a meningococcal vaccine at least two weeks prior to receipt of eculizumab, or received antibiotic prophylaxis to reduce the risk of developing a meningococcal infection prior to the development of adequate vaccine-induced immunity. Additionally, some physicians chose to continue to administer antibiotics to patients even after two weeks elapsed from administration of the meningococcal vaccine.

To date, no reports of *N. meningitidis* infection have been reported in patients enrolled in Studies C08-002 and C08-003. One patient with aHUS in Study C09-001r, developed a serious *N. meningitidis* infection after completion of the study.

Please refer to Section 7.7 for a comprehensive analysis and discussion of this safety issue.

Reviewer comment: The proposed labeling includes a box warning instructing healthcare providers to vaccinate patients with a meningococcal vaccine 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. The proposed label also includes a contraindication for Soliris in patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection. Additionally, the warnings section informs physicians that although the benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving Soliris have not been established, some patients with aHUS enrolled in clinical studies received antibiotic prophylaxis.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study C08-002 and Study C08-003

In these single arm prospective studies, a total of 36 of 37 patients (97%) experienced a treatment emergent adverse event. Table 34 lists the adverse events that occurred in at least 4 (11%) of the 37 patients enrolled in Studies C08-002 and C08-003. The most frequently reported adverse reactions ($\geq 15\%$ combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

Table 34: Per Patient Incidence of Selected Adverse Events in Adult and Adolescent Patients Enrolled in Studies C08-002 and C08-003

MedDRA ver. 11.0 Preferred Term n (%)	Number (%) of Patients		
	C08-002 (N=17)	C08-003 (N=20)	Total (N=37)
Vascular Disorders			
Hypertension ^a	8(47)	5 (25)	13 (35)
Hypotension	0	1 (5)	1 (3)
Infections and Infestations			
Upper respiratory tract infection ^b	5 (29)	8 (40)	13(35)
Urinary tract infection	4 (24)	2 (10)	6 (16)
Gastrointestinal Disorders			
Diarrhea	6 (35)	6 (30)	12 (32)
Vomiting	5 (29)	3 (15)	8 (22)
Nausea	4 (24)	3 (15)	7 (19)
Abdominal pain	0	4 (20)	4 (11)
Peritonitis	0	1 (5)	1 (3)
Nervous System Disorders			

MedDRA ver. 11.0 Preferred Term n (%)	Number (%) of Patients		
	C08-002 (N=17)	C08-003 (N=20)	Total (N=37)
Headache	7 (41)	4 (20)	11 (30)
Convulsion	1 (6)	0	1 (3)
Reversible posterior leukoencephalopathy syndrome	1 (6)	0	1 (3)
Blood and Lymphatic System Disorders			
Anemia	6 (35)	3 (15)	9 (24)
Leukopenia	4 (24)	2 (10)	6 (16)
Psychiatric Disorders			
Insomnia	4 (24)	1 (5)	5 (14)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	2 (12)	3 (15)	5 (14)
Pharyngolaryngeal pain	1 (6)	4 (20)	5 (14)
General Disorders and Administration Site Conditions			
Fatigue	3 (18)	1 (5)	4 (11)
Peripheral edema	3 (18)	1 (5)	4 (11)
Pyrexia	3 (18)	1 (5)	4 (11)
Ear and Labyrinth Disorders			
Vertigo	1 (6)	3 (15)	4 (11)
Musculoskeletal and Connective Tissue Disorders			

MedDRA ver. 11.0 Preferred Term	Number (%) of Patients			
	n (%)	C08-002 (N=17)	C08-003 (N=20)	Total (N=37)
Pain in extremity		1 (6)	3 (15)	4 (11)

^a includes the preferred terms hypertension, accelerated hypertension, and malignant hypertension.

^b includes the preferred terms upper respiratory tract infection and nasopharyngitis.

In general, the incidence of adverse events was comparable in both studies. *Reviewer note: because Studies C08-002 and C08-003 are single arm studies that enrolled patients with comorbid conditions such as renal impairment and hypertension who were being treated with multiple concomitant medications, it is not possible to establish causality for many adverse events, such as hypertension, fatigue, headache, and anemia.*

Investigators were instructed to grade adverse events as "severe" if "they interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment." The protocols for Studies C08-002 and C08-003 stated that most severe adverse events are "incapacitating." Table 35 lists treatment adverse events that occurred in two or more patients in both studies combined, and severe adverse events that occurred in one or more patients. A total of 12/37 patients (30%) had a severe adverse event in both studies combined [8 (47%) of patients in Study C08-002 and 4 (20%) in Study C08-003]. With the exception of severe hypertension, which was reported in 2 patients, each type of severe adverse event occurred in a single patient.

Table 35: Per patient Incidence of treatment emergent adverse events, broken down by severity, in prospective aHUS Studies.

Preferred Term	Study C08-002				Study C08-003				Both Prospective Studies			
	All Grades		Severe		All Grades		Severe		All Grades		Severe	
	n	%	n	%	n	%	n	%	n	%	n	%
Diarrhea	6	35	0	0	6	30	1	5	12	32	1	3
Headache	7	41	1	6	4	20	0	0	11	30	1	3
Hypertension	4	24	2	12	5	25	0	0	9	24	2	5
Anemia	6	35	1	6	3	15	0	0	9	24	1	3
Vomiting	5	29	0	0	3	15	1	5	8	22	1	3
Nasopharyngitis	1	6	0	0	7	35	0	0	8	22	0	0
Nausea	4	24	0	0	3	15	0	0	7	19	0	0
Upper Respiratory	4	24	0	0	3	15	0	0	7	19	0	0

Preferred Term	Study C08-002				Study C08-003				Both Prospective Studies			
	All Grades		Severe		All Grades		Severe		All Grades		Severe	
	n	%	n	%	n	%	n	%	n	%	n	%
Tract Infection												
Renal Impairment	4	24	1	6	2	10	0	0	6	16	1	3
Leukopenia	4	24	0	0	2	10	0	0	6	16	0	0
Urinary Tract Infection	4	24	0	0	2	10	0	0	6	16	0	0
Cough	2	12	0	0	3	15	0	0	5	14	0	0
Insomnia	4	24	0	0	1	5	0	0	5	14	0	0
Pharyngolaryngeal Pain	1	6	0	0	4	20	0	0	5	14	0	0
Pyrexia	3	18	0	0	1	5	0	0	4	11	0	0
Fatigue	3	18	1	6	1	5	0	0	4	11	1	3
Abdominal Pain	0	0	0	0	4	20	0	0	4	11	0	0
Peripheral Edema	3	18	0	0	1	5	0	0	4	11	0	0
Pain In Extremity	1	6	0	0	3	15	0	0	4	11	0	0
Vertigo	1	6	0	0	3	15	0	0	4	11	0	0
Epistaxis	2	12	0	0	1	5	1	5	3	8	1	3
Asthenia	1	6	0	0	2	10	0	0	3	8	0	0
Back Pain	1	6	0	0	2	10	0	0	3	8	0	0
Blood Lactate Dehydrogenase Increased	2	12	0	0	1	5	0	0	3	8	0	0
Dizziness	3	18	0	0	0	0	0	0	3	8	0	0
Dyspnea	3	18	0	0	0	0	0	0	3	8	0	0
Hypersensitivity	0	0	0	0	3	15	0	0	3	8	0	0
Lymphopenia	0	0	0	0	2	10	0	0	2	5	0	0
Muscle Spasms	2	12	0	0	1	5	0	0	3	8	0	0
Malignant Hypertension	2	12	1	6	0	0	0	0	2	5	1	3
Abdominal Pain Upper	1	6	0	0	1	5	0	0	2	5	0	0
Accelerated Hypertension	2	12	0	0	0	0	0	0	2	5	0	0
Aphthous Stomatitis	0	0	0	0	2	10	0	0	2	5	0	0
Arthralgia	1	6	0	0	1	5	0	0	2	5	0	0
Basophil Count Increased	0	0	0	0	2	10	0	0	2	5	0	0
Erythema	2	12	0	0	0	0	0	0	2	5	0	0
Gastroenteritis	1	6	0	0	1	5	0	0	2	5	0	0
Hematuria	2	12	0	0	0	0	0	0	2	5	0	0
Hemorrhoids	1	6	0	0	1	5	0	0	2	5	0	0

Preferred Term	Study C08-002				Study C08-003				Both Prospective Studies			
	All Grades		Severe		All Grades		Severe		All Grades		Severe	
	n	%	n	%	n	%	n	%	n	%	n	%
Herpes Zoster	2	12	0	0	0	0	0	0	2	5	0	0
Hyperkalemia	1	6	0	0	1	5	0	0	2	5	0	0
Hypokalemia	2	12	0	0	0	0	0	0	2	5	0	0
Hypomagnesemia	2	12	0	0	0	0	0	0	2	5	0	0
Iron Deficiency Anemia	1	6	0	0	1	5	0	0	2	5	0	0
Joint Swelling	2	12	0	0	0	0	0	0	2	5	0	0
Myalgia	1	6	0	0	1	5	0	0	2	5	0	0
Nasal Congestion	1	6	0	0	1	5	0	0	2	5	0	0
Neutropenia	1	6	0	0	1	5	0	0	2	5	0	0
Edema	1	6	0	0	1	5	0	0	2	5	0	0
Pain	1	6	0	0	1	5	0	0	2	5	0	0
Proteinuria	1	6	0	0	1	5	0	0	2	5	0	0
Pruritus	0	0	0	0	2	10	0	0	2	5	0	0
Rash	2	12	0	0	0	0	0	0	2	5	0	0
Reticulocyte Count Increased	1	6	0	0	1	5	0	0	2	5	0	0
Rhinorrhea	1	6	0	0	1	5	0	0	2	5	0	0
Seasonal Allergy	1	6	0	0	1	5	0	0	2	5	0	0
Sinusitis	1	6	0	0	1	5	0	0	2	5	0	0
Toothache	2	12	0	0	0	0	0	0	2	5	0	0
Cholelithiasis	1	6	1	6	0	0	0	0	1	3	1	3
Convulsion	1	6	1	6	0	0	0	0	1	3	1	3
Hypotension	0	0	0	0	1	5	1	5	1	3	1	3
Peritonitis	0	0	0	0	1	5	1	5	1	3	1	3
Renal Failure Chronic	0	0	0	0	1	5	1	5	1	3	1	3
Reversible Posterior Leukoencephalopathy Syndrome	1	6	1	6	0	0	0	0	1	3	1	3
Systemic Lupus Erythematosus	1	6	1	6	0	0	0	0	1	3	1	3
Vein Disorder	0	0	0	0	1	5	1	5	1	3	1	3

Study C09-001r

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. Twenty-two of 30 patients (73%) in Study C09-001r experienced at least one treatment emergent adverse event. Infections were reported in 60% of patients; the most common individual infectious adverse event was upper respiratory tract infection (20%), followed by nasopharyngitis (10%), and flu (10%). Gastrointestinal disorders occurred in 43% of patients; the most frequent gastrointestinal adverse events were diarrhea (27%) and vomiting (23%). As Table 36 indicates, few adverse events were considered to be severe.

Table 36: Per Patient Incidence of treatment emergent adverse events, broken down by severity, in Study C09-001r

System Organ Class	Preferred Term	All Grades N = 30		Severe N = 30	
		n	%	n	%
General disorders and administration site conditions	Pyrexia	9	30	1	3
	Asthenia	2	7	0	0
	Catheter site hematoma	2	7	0	0
	Fatigue	2	7	0	0
	Infusion site pain	2	7	0	0
	Edema	2	7	0	0
	Pain	2	7	0	0
	Multi-organ failure	1	3	1	3
Gastrointestinal disorders	Diarrhea	8	27	0	0
	Vomiting	7	23	0	0
	Abdominal pain	3	10	0	0
	Nausea	3	10	0	0
	Peritonitis	1	3	1	3
Respiratory, thoracic and mediastinal disorders	Cough	7	23	0	0
Infections and infestations	Upper respiratory tract infection	6	20	1	3
	Influenza	3	10	0	0
	Nasopharyngitis	3	10	0	0
	Central line infection	2	7	1	3
	Fungal infection	2	7	1	3
	Pneumonia	2	7	1	3

System Organ Class	Preferred Term	All Grades N = 30		Severe N = 30	
		n	%	n	%
	Cytomegalovirus infection	2	7	0	0
	Klebsiella infection	2	7	0	0
	Pseudomonas infection	2	7	0	0
	Rhinitis	2	7	0	0
	Sinusitis	2	7	0	0
	Staphylococcal infection	2	7	0	0
	Bronchopulmonary aspergillosis	1	3	1	3
	Respiratory tract infection	1	3	1	3
	Sepsis	1	3	1	3
	Urinary tract infection	1	3	1	3
	Nervous system disorders	Headache	5	17	0
Carotid artery dissection		1	3	1	3
Cerebrovascular accident		1	3	1	3
Respiratory, thoracic and mediastinal disorders	Nasal congestion	4	13	0	0
	Rhinorrhea	2	7	0	0
Cardiac disorders	Tachycardia	4	13	0	0
Blood and lymphatic system disorders	Anemia	3	10	0	0
	Intravascular hemolysis	2	7	0	0
	Neutropenia	2	7	0	0
Psychiatric disorders	Insomnia	3	10	0	0
Ear and labyrinth disorders	Ear pain	2	7	0	0
Eye disorders	Eyelid edema	2	7	0	0
Metabolism and nutrition disorders	Decreased appetite	2	7	0	0
	Dehydration	2	7	0	0
	Fluid retention	2	7	0	0
	Hyperphosphatemia	2	7	0	0
	Hypokalemia	2	7	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	2	7	0	0
	Osteopenia	2	7	0	0
Skin and subcutaneous tissue disorders	Petechiae	2	7	0	0
	Rash	2	7	0	0
Vascular disorders	Hypertension	2	7	0	0
Immune system disorders	Acute graft versus host disease in intestine	1	3	1	3

Study C09-001r included 19 pediatric patients less than 18 years of age. The adverse event profile in pediatric patients enrolled in Study C09-001r was similar to that observed in adult and adolescent patients enrolled in the prospective studies, with the exception of adverse events that are often observed more frequently in children. The most common (>10%) adverse events occurring in pediatric patients are presented in Table 37. Pyrexia (9/19, or 47%), cough (5/19, or 26%), upper respiratory tract infection (5/19, or 26%), nasal congestion (4/21%), and tachycardia (4/21%) occurred in more than two pediatric patients at an incidence at least 5% greater than that seen in adults and adolescents in the prospective studies. *Reviewer comment: differences in the incidences of adverse events between adult and pediatric patients should be interpreted with caution due to the small patient numbers.*

Table 37: Comparison of PPI Adverse Events in Pediatric and Adult Patients in Retrospective Study¹

Preferred Term	Pediatric n = 19		Adult n = 11		Total n = 30	
	n	%	n	%	n	%
Pyrexia	9	47	0	0	9	30
Diarrhea	6	32	2	18	8	27
Cough	5	26	2	18	7	23
Vomiting	4	21	3	27	7	23
Upper respiratory tract infection	5	26	1	9	6	20
Headache	2	11	3	27	5	17
Nasal congestion	4	21	0	0	4	13
Tachycardia	4	21	0	0	4	13
Abdominal pain	2	11	1	9	3	10
Anemia	2	11	1	9	3	10
Influenza	2	11	1	9	3	10
Nasopharyngitis	2	11	1	9	3	10
Insomnia	1	5	2	18	3	10
Nausea	1	5	2	18	3	10
Central line infection	2	11	0	0	2	7
Decreased appetite	2	11	0	0	2	7
Dehydration	2	11	0	0	2	7
Ear pain	2	11	0	0	2	7
Eyelid edema	2	11	0	0	2	7
Hyperphosphatemia	2	11	0	0	2	7

Preferred Term	Pediatric n = 19		Adult n = 11		Total n = 30	
	n	%	n	%	n	%
Infusion site pain	2	11	0	0	2	7
Edema	2	11	0	0	2	7
Osteopenia	2	11	0	0	2	7
Pain	2	11	0	0	2	7
Rash	2	11	0	0	2	7
Rhinorrhea	2	11	0	0	2	7
Arthralgia	0	0	2	18	2	7
Cytomegalovirus infection	0	0	2	18	2	7
Hypokalemia	0	0	2	18	2	7
Pseudomonas infection	0	0	2	18	2	7

TEAEs occurring in at least 2 patients in the pediatric or adult subgroup in Study C09-001r.

Table 38 provides a comparison of adverse events in different pediatric age groups.

Table 38: Comparison of Adverse Events in Pediatric Patients by Age Subgroup – Retrospective Study C09-001r

Preferred Term	< 2 years n = 5		2 to < 12 years n = 10		12 to < 18 years n = 4		All Pediatric Patients n = 19	
	n	%	n	%	n	%	n	%
Pyrexia	4	80	4	40	1	25	9	47
Diarrhea	1	20	4	40	1	25	6	32
Cough	3	60	2	20	0	0	5	26
Upper respiratory tract infection	2	40	3	30	0	0	5	26
Vomiting	2	40	1	10	1	25	4	21
Nasal congestion	2	40	2	20	0	0	4	21
Tachycardia	2	40	2	20	0	0	4	21
Abdominal pain	0	0	1	10	1	25	2	11
Anemia	2	40	0	0	0	0	2	11
Headache	0	0	2	20	0	0	2	11
Influenza	1	20	1	10	0	0	2	11
Nasopharyngitis	0	0	1	10	1	25	2	11

Preferred Term	< 2 years n = 5		2 to < 12 years n = 10		12 to < 18 years n = 4		All Pediatric Patients n = 19	
	n	%	n	%	n	%	n	%
Central line infection	1	20	1	10	0	0	2	11
Decreased appetite	1	20	0	0	1	25	2	11
Dehydration	1	20	1	10	0	0	2	11
Ear pain	1	20	1	10	0	0	2	11
Eyelid edema	1	20	1	10	0	0	2	11
Hyperphosphatemia	0	0	1	10	1	25	2	11
Infusion site pain	1	20	1	10	0	0	2	11
Edema	0	0	2	20	0	0	2	11
Osteopenia	0	0	1	10	1	25	2	11
Pain	1	20	1	10	0	0	2	11
Rash	2	40	0	0	0	0	2	11
Rhinorrhea	1	20	1	10	0	0	2	11

¹ TEAEs occurring in at least 2 pediatric patients in Study C09-001r.

Integrated Summary of Adverse Events

Table 39 provides a tabular summary of adverse events that were reported as severe in at least one patient or occurred at a per patient incidence of at least 5% in Studies C08-002, C08-003, and C09-001r combined. The most common adverse events reported across all studies were diarrhea, headache, vomiting, pyrexia, upper respiratory tract infection, hypertension, cough, and anemia.

Table 39: Integrated Summary of Adverse Events for Study C08-002, C08-003 and C00-01r

System Organ Class	Preferred Term	All Adverse Events N = 67		Severe Adverse Events N = 67	
		n	%	n	%
Gastrointestinal Disorders	Diarrhea	21	31	1	2
	Vomiting	15	22	1	2
	Nausea	10	15	0	0
	Abdominal Pain	7	10	0	0
	Peritonitis	2	3	2	3
Nervous System Disorders	Headache	16	24	1	2
	Dizziness	4	6	0	0

System Organ Class	Preferred Term	All Adverse Events N = 67		Severe Adverse Events N = 67	
		n	%	n	%
	Convulsion	2	3	1	2
General Disorders And Administration Site Conditions	Pyrexia	14	21	1	2
	Fatigue	6	9	1	2
	Asthenia	5	8	0	0
	Edema	4	6	0	0
	Edema Peripheral	4	6	0	0
	Pain	4	6	0	0
Infections And Infestations	Upper Respiratory Tract Infection	13	19	1	2
	Nasopharyngitis	11	16	0	0
	Urinary Tract Infection	7	10	1	2
	Sinusitis	4	6	0	0
	Pneumonia	3	5	1	2
	Influenza	3	5	0	0
	Rhinitis	3	5	0	0
	Central Line Infection	2	3	1	2
Blood And Lymphatic System Disorders	Fungal Infection	2	3	1	2
	Anemia	12	18	1	2
	Leukopenia	6	9	0	0
	Neutropenia	4	6	0	0
Respiratory, Thoracic And Mediastinal Disorders	Lymphopenia	3	5	0	0
	Cough	12	18	0	0
	Nasal Congestion	6	9	0	0
	Pharyngolaryngeal Pain	6	9	0	0
	Epistaxis	4	6	1	2
	Rhinorrhea	4	6	0	0
	Dyspnea	3	5	0	0
Vascular Disorders	Hypertension	11	16	2	3
	Malignant Hypertension	2	3	1	2
	Accelerated Hypertension	2	3	0	0
Psychiatric Disorders	Insomnia	8	12	0	0
Renal And Urinary Disorders	Renal Impairment	6	9	1	2
	Renal Failure Chronic	2	3	1	2
Cardiac Disorders	Tachycardia	4	6	0	0

System Organ Class	Preferred Term	All Adverse Events N = 67		Severe Adverse Events N = 67	
		n	%	n	%
Ear And Labyrinth Disorders	Vertigo	4	6	0	0
Metabolism And Nutrition Disorders	Hypokalemia	4	6	0	0
	Fluid Retention	3	5	0	0
	Hyperkalemia	3	5	0	0
	Hyperphosphatemia	3	5	0	0
Musculoskeletal And Connective Tissue Disorders	Arthralgia	4	6	0	0
	Back Pain	4	6	0	0
	Pain In Extremity	4	6	0	0
	Muscle Spasms	3	5	0	0
	Myalgia	3	5	0	0
Skin And Subcutaneous Tissue Disorders	Rash	4	6	0	0
Immune System Disorders	Hypersensitivity	3	5	0	0
Investigations	Blood Lactate Dehydrogenase Increased	3	5	0	0

7.4.2 Laboratory Findings

A pooled analysis of hematologic parameters in patient enrolled in Studies C08-002, C08-003, and C09-001r did not reveal any clinically important safety signals. Of the 37 patients enrolled in the two studies, 27 patients had normal white blood cell counts at baseline, and 9 patients had leukopenia. During the course of the study, 20 of the 27 patients with WBC counts in the normal range at baseline developed brief episodes of leukopenia. In the remaining five patients, leukopenia occurred in patients using immunosuppressive agents for the prevention of renal allograft rejection. Febrile neutropenia and neutropenic infections were not reported. Similarly, clinically relevant lymphopenia did not occur in patients enrolled in these studies.

Hepatic Parameters

The majority of patients in the prospective studies had normal liver function parameters at baseline. No patients with normal hepatic function at baseline displayed adverse changes to hepatic function parameters during the study period. Three of the 4 patients with elevated alanine amino transferase and aspartate aminotransferase at baseline had improvement in these parameters during study treatment.

Five patients who had normal albumin levels at baseline had a single low measurement during the study, which was followed by normal albumin measurements. Fourteen of 37 patients developed transient hypoproteinemia while receiving eculizumab; however, total serum protein returned to the normal range in all patients.

Other Serum Chemistries

Of 32 patients with abnormal BUN at baseline, BUN normalized in 11 patients. One patient had transient elevation in serum glucose, but this patient also received concomitant corticosteroids.

As expected in patients with renal impairment, abnormalities in serum electrolytes were observed during these studies; however, no electrolyte abnormalities of sufficient severity to cause adverse events occurred, and there was no apparent trend for worsening in these parameters with introduction of eculizumab.

7.4.3 Vital Signs

Vital signs, including heart rate, blood pressure, and weight, were monitored regularly in the prospective studies. Analysis of vital signs did not uncover a pattern for clinically relevant adverse changes in heart rate or weight during the study period.

Hypertension was a comorbid condition requiring one or more antihypertensive agents for 33 of 37 (89%) patients at baseline. In Studies C08-002 and C08-003, 13 patients (35%) experienced at least one hypertension-related adverse event, but the relationship between hypertension and eculizumab therapy is unclear in the background of renal impairment and pre-existing hypertension. Furthermore, hypertension was manageable with adjustments to antihypertensive medications when necessary, and did not result in discontinuation of eculizumab.

7.4.4 Electrocardiograms (ECGs)

In Study C08-002, monitoring with 12-lead ECGs occurred at least once during the treatment and extension periods. Eight of 17 patients had abnormal ECG results on at least one assessment. However, none of the abnormalities were considered clinically significant, nor did a change in patient management occur as a result of ECG abnormalities observed.

In Study C08-003, 12-lead ECGs were obtained in all patients at least once during the study period. ECGs displayed abnormal results in 7 patients (35%) at baseline, and 8 patients (40%) had at least one abnormal ECG result during treatment with eculizumab. However, none of the ECG abnormalities were considered clinically significant.

ECG data was not collected in the retrospective study (C09-001r).

7.4.5 Special Safety Studies/Clinical Trials

7.4.6 Immunogenicity

See Section 4.4 of this review for a brief discussion of results of HAHA immunogenicity assays. For a more detailed review, please refer to the FDA Clinical Pharmacology Review for this sBLA, conducted by Bahru Habtemariam, PharmD.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No formal analyses of dose dependency for adverse events were performed. There were not pre-specified dose modifications for adverse events.

7.5.2 Time Dependency for Adverse Events

No formal analyses for time dependency for adverse events were performed.

7.5.3 Drug-Demographic Interactions

Approximately 65% of patients enrolled in studies C08-002A and C08-003 were female. There were no major differences in the incidence of adverse events or serious adverse events based on gender. An analysis of the impact of age on the safety of eculizumab for the treatment of aHUS is presented in Section 7.4.1 of this review.

7.5.4 Drug-Disease Interactions

No formal safety analyses of drug-disease interactions with eculizumab were conducted.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction clinical studies of eculizumab were conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity data were submitted with this application.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of eculizumab in pregnant women. Because eculizumab is a recombinant IgG molecule, it is expected to cross the placenta. In animal studies, administration of murine anti-C5 antibody at doses 2-8 times the human dose resulted in increased rates of developmental abnormalities and dead and moribund offspring. In a small case series of pregnant women with PNH, most women who received eculizumab delivered healthy infants, but long-term follow-up data is not available.

7.6.3 Pediatrics and Assessment of Effects on Growth

Please see the assessment of safety for the pediatric subset of patients (n = 19) enrolled in Study C09-001r in Section 7.3 for information regarding adverse events observed in the pediatric population. As noted previously, the assessment of safety in pediatric patients is limited by the small number of pediatric patients enrolled and the retrospective nature of Study C09-001r. Because, like all retrospective studies, this study did not pre-specify the methods for capturing adverse events, the results of this safety analysis from this study should be interpreted with caution.

Analysis of the impact of eculizumab therapy on developmental parameters such as weight is complicated by the lack of a comparator arm, the chronic nature of aHUS (which is likely to adversely impact development), and co-morbid renal impairment (which can result in fluid shifts). The median change in weight in the 19 pediatric patients enrolled in the retrospective study, as calculated by the difference between the last recorded weight and the baseline weight, was 1.4 kg (range: **- 7 kg to 11.2 kg**). This median change occurred over a median of 197 study days (range 8 days to 483 days).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses were reported in the studies submitted with this application. Because of the REMS requirement for physician registration to obtain eculizumab, as well as the mechanism of action and mode of administration of eculizumab, there is negligible potential for this drug to be used for non-therapeutic purposes. There is no evidence that discontinuation of eculizumab would result in withdrawal or rebound signs or symptoms.

Because eculizumab affects the balance of complement activation, it is possible that its discontinuation would make patients more vulnerable to aHUS exacerbations than they would be if eculizumab treatment was continued. Section 6.1.9 describes the occurrence of aHUS exacerbations following discontinuation of eculizumab in four patients enrolled retrospective study C09-001r.

7.7 Additional Submissions / Safety Issues

On July 20, 1011, in accordance with 21 CFR 314.50(d)(5)(vi)(b), the applicant submitted a 120-day Safety Update Report. This submission included updated survival and adverse event data for Study C08-002 and Study C08-003 through March 15, 2011. This safety update included an additional 26.9 weeks of follow up data for Study C08-002 and 21.1 weeks for Study C08-003. The safety update also included a summary of serious adverse events spontaneously reported by treating physicians during the treatment period for patients enrolled in Study C09-011r.

Prospective Studies

At the time of the safety update, the median duration of treatment was 64 weeks for patients enrolled in Studies C08-002 and C08-003. Twenty-eight patients (76%) had been treated for more than one year. Of the patients who had been treated for less than a year, five patients had discontinued treatment by the data cut-off date for the original submission, and the remaining four patients had been treated for 322 to 350 days. No additional patients in either study discontinued eculizumab treatment at the time of the safety update.

The types of adverse events reported in the safety update were generally similar to those reported in the original submission, but the incidence of adverse events was greater. Notably, the percentage of patients who experienced hypertension rose from 24% to 47% in Study C08-002, and from 25% to 35% in study C08-003. All patients who experienced hypertension had a history of hypertension prior to beginning therapy with eculizumab. Nausea, vomiting, hypotension, headache, and nasopharyngitis were experience by four or more additional patients each. A total of 16 (43%) patients had at least one severe adverse event at the update, compared to 12 (32%) at the time of submission.

At the time of data cut-off for the original submission and the safety update, no patients in either study had died. The safety update contained reports of 24 additional SAEs experienced by 14 patients. Seven patients for whom SAEs had not been reported in the original study reports experienced SAEs (2 in study C08-002 and 5 in Study C08-003). Based on the updated safety data, 100% (17/17) of patients in Study C08-002 experienced an SAE, and 50% (10/20) of patients in Study C08-003 experienced an SAE. Infectious adverse events accounted for the largest increase in the number of patients reporting SAEs. Five patients, all enrolled in Study C08-003, reported

additional SAEs of infections. These infections consisted of: influenza, pneumonia, norovirus, chronic hepatitis e, and Q fever. The incidence of patients reporting SAEs for vascular disorders increased from 8/37 (22%) at the original data cut-off date to 10/37 (27%) in the safety update; a venous thrombosis of the lower extremity developed in one patient, and a venous embolism occurred in another patient. With the exception of ongoing worsening of hypertension (patient 196-001) and the venous thromboembolism (198-002), all SAEs had resolved by the data cut-off date for the safety update.

Reviewer comment: The increased incidence of treatment emergent adverse events and serious adverse events reported in the safety update is notable. However, the additional adverse events reported in the safety update occurred in patients that tend to have multiple serious medical comorbidities (such as hypertension and chronic renal disease) over approximately six months. Additionally, many patients with aHUS require immunosuppressive therapy to prevent renal allograft rejection, which predisposes them to infection. Therefore, the increase in adverse events does not appear disproportionately high compared to what might be expected in this patient population. Furthermore, no patients elected to discontinue therapy due to an adverse event during this six month period. Based on review of the adverse event data included in this safety update, the safety profile of eculizumab in patients with aHUS remains unchanged.

Retrospective Study

The safety update also included narratives for SAEs spontaneously reported by treating physicians of patients enrolled in Study C09-011r during the original study period. Review of these narratives did not uncover additional safety signals that were not evident from reviewing the data included in the original submission.

Other Safety Analyses

Neisseria meningitidis infections

The applicant estimates that the rate of meningococcal infection in eculizumab-treated patients is approximately 0.5 cases per 100 patient years. The applicant reported that as of June 30, 2011, there have been 23 cases of infections due to *Neisseria meningitidis* in eculizumab-treated patients. Three cases occurred in clinical trials, and 20 were reported during the postmarketing period. Twenty patients (87%) who developed *Neisseria meningitidis* infections received eculizumab for the treatment of PNH, one patient had aHUS, and 1 patient had neuromyelitis optica. The median age at the time of infection was 24 (range 15 – 54), and 14 (61%) were female. Four patients died, two patients recovered with sequelae, and 17 patients recovered fully. The majority of cases occurred in vaccinated patients, and were caused by strains not covered by the current quadravalent vaccine (serotype B).

At the time of reporting, no patients in the prospective aHUS studies developed a meningococcal infection. One aHUS patient enrolled in the retrospective aHUS study,

C09-001r, developed meningococemia after the study was completed. According to the applicant, this patient was also being treated with immunosuppressants for prophylaxis of renal allograft rejection while receiving eculizumab.

Malignancies

At the request of FDA, the applicant provided a cumulative summary of malignancy adverse events that have been reported during the post-marketing period, from March 16, 2007 through April 1 2011. During this period, a total of 109 neoplasms, (51 solid tumors, 36 hematologic malignancies, and 12 non-malignant neoplasms) were reported. According to the applicant, this represents a frequency of 3.1 malignancies per 100 patient years of eculizumab exposure. These malignancies primarily occurred in patients with PNH. The most frequent malignancy adverse event were hematologic. Myelodysplastic syndrome (MDS, in 19 cases) was the most common malignancy, followed by acute myeloid leukemia (8 cases), basal cell carcinoma (7 cases), acute leukemia (4 cases), leukemia (4 cases), thyroid cancer (3 cases) and squamous cell carcinoma (3 cases). Lung adenocarcinoma, malignant melanoma, malignant neoplasm progression, metastatic pancreatic carcinoma, and skin cancer were reported in two patients apiece. Fifty of the malignancy adverse events either occurred in a patient with a prior history of the malignancy, or represented either disease recurrences or disease progression.

Reviewer comment: This report indicates that 47 patients (virtually all with PNH) developed a new malignancy (or premalignant condition, in the case of MDS) over a four year treatment period. The most recent periodic safety update report (PSUR) for Soliris estimated that 1,666 patients received Soliris in the prior year. It is traditionally cited that 5-15 % of patients with PNH develop hematologic malignancies [Harris J et al. 1999 Leukemia and Lymphoma Vol 32 (5-6)]. Patients with PNH are at increased risk for the development of MDS, which in turn may lead to the development of acute leukemias, most commonly AML. Therefore, the frequency of malignancies reported in patients receiving eculizumab appears to be consistent with the frequency of malignancies that would be expected to occur in patients with PNH.

8 POSTMARKET EXPERIENCE

In the most recent PSUR, covering the reporting period from April 2, 2010 to April 1, 2011, the applicant indicated that approximately 1,666 patients (including 47 patients treated in clinical trials) were treated with eculizumab. A total of 5480 adverse events occurring in 1,749 patients were reported spontaneously, in clinical studies, or in the literature during the 12 month period. A total of 502 serious unlisted adverse reactions, 51 serious listed adverse reactions, 928 non-serious unlisted adverse reactions, and, 268 non-serious listed adverse reactions were reported. A total of 68 deaths were reported during this reporting period, none in clinical studies. Two deaths occurred secondary to *Neisseria meningitidis* infections, and the remainder either lacked a

temporal relationship to eculizumab, were confounded by concurrent conditions, or lacked sufficient details to establish causality.

During the reporting period there were eight reported cases of *Neisseria meningitidis*, including the two fatal cases. Three additional cases of *Neisseria meningitidis*, one fatal, were reported between April 1, 2011 and May 27, 2011. As described in Section 7.7 of this review, there have been a total of 23 reported cases of *Neisseria meningitidis* infection identified in patients who have received eculizumab over the course of its clinical development and postmarketing experience.

Reviewer comment: Soliris is used in the treatment of patients who typically have multiple concurrent medical conditions that places them at risk for the development of adverse events related to these conditions. Additionally, patients treated with Soliris usually receive more than one additional concomitant medication. A review of the listed and unlisted adverse events reported in this PSUR did not uncover a new safety signal of concern for which a reasonable possibility of a causal role for eculizumab could be established.

9 Appendices

9.1 Literature Review/References

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Taylor CM, Machin S, Wigmore SJ, Goodship TH, working party from the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. *Br J Haematol* 2010 Jan;148(1):37-47.

Tsai HM. The molecular biology of thrombotic microangiopathy. *Kidney Int.* 2006 Jul;70(1):16-23.

Zimmerhackl L, Besbas N, Jungraithmayr T, van de Kar N, Karch H, et al. Epidemiology, clinical presentation, and pathophysiology of atypical and recurrent hemolytic uremic syndrome. *Semin Thromb Hemost* 2006 Mar;32(2):113-20.

9.2 Labeling Recommendations

At the time of completion of this review, text for the proposed label had not been finalized. All sections of the proposed label were revised for clarity, brevity, and consistency, and some sections were reorganized to improve understandability and readability. Only clinically-relevant, substantive content changes will be discussed in this review.

9.2.1 Box Warning

- The label proposed by the sponsor (b) (4)

- An instruction was added for healthcare providers to comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Text was added to inform patients and healthcare providers that fatal and life-threatening meningococcal infections have occurred in Soliris-treated patients (as opposed to (b) (4))

9.2.2 Indications and Usage

- Because Soliris has not been studied in the more common forms of Hemolytic Uremic Syndrome (which may have a different underlying pathophysiology than aHUS), a limitation of use was added stating that Soliris is not indicated for the treatment of patients with typical hemolytic uremic syndrome.

9.2.3 Dosage and Administration

- Added text instructing vaccination of patients according to current ACIP guidelines to reduce the risk of serious infection

9.2.4 Contraindications

- The label proposed by the applicant  (b) (4)

 The clinical team modified this to contraindicate Soliris in patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection.

9.2.5 Warnings and Precautions

- Because the risks of delaying Soliris treatment may in some cases be greater than the risks of developing a meningococcal infection in an unvaccinated patient, the clinical team added language to instruct clinicians that if urgent Soliris therapy is indicated in an unvaccinated patient, to administer the meningococcal vaccine as soon as possible.
- Added the following language to provide information about the administration of prophylactic antibiotics in the aHUS clinical studies: **"some patients with aHUS** received antibiotics for prophylaxis of meningococcal infection for 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.**"
- In section 5.3, added information regarding the potential risk of the development of serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae type b (Hib)*. Additionally, instructed clinicians to administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae type b (Hib)* infections according to ACIP guidelines.

-  (b) (4)



9.2.6 Adverse Reactions

- Added text to provide information that one Soliris-treated patient with aHUS enrolled in the retrospective study died during the post-study follow-up period.
- The clinical team also reorganized the presentation of adverse events so that all pediatric (less than 18 years of age) were included in the adverse events table for the retrospective study.

9.2.7 Use in Specific Populations

- The Pediatric and Maternal Health Staff recommended that the label be modified to include the following text:

Human Data

Limited published literature describing a case report and a small case series in pregnant women with PNH treated with Soliris report that most women delivered healthy infants, although long-term follow-up data is not available. The duration of Soliris exposure was not consistent throughout gestation. An increased dose of Soliris was often required to block complement during later stages of these pregnancies as compared to the non-pregnant state. No data is available on the use of Soliris in pregnant women with aHUS.

Reviewer comment: at the time of completion of this review, the clinical review team had not decided whether to include this text in the label, because of the limited extent of information available.

- For emphasis, repeated instructions for clinicians to administer vaccinations for the prevention of infections due to *N. meningitidis*, *S. pneumoniae*, and *H. influenza* type b (Hib) according to ACIP guidelines.

9.2.8 Clinical Studies Section

- The label proposed by the applicant originally contained (b) (4) that were subsequently deleted by the FDA clinical team:

(b) (4)

(b) (4)

(b) (4)

[REDACTED] (b) (4)

- [REDACTED] (b) (4)

- [REDACTED] (b) (4)

- [REDACTED] (b) (4)

- Presentation of pediatric data in the retrospective study was modified to include data from patients < 18 years of age by age subgroup (, instead [REDACTED] (b) (4).
- In order to provide information regarding the durability of improvement in renal function parameters, Information regarding the durability of improvement in eGFR was added.

9.3 Advisory Committee Meeting

This sBLA was not the subject of an advisory committee meeting. As part of the review of this sBLA, the clinical review team sought advice from three consultants with expertise in pediatric nephrology and pediatric hematology. These consultants were designated as Special Government Employees and were cleared for conflict of interest by the Division of Advisory Committee and Consultant Management at CDER prior to discussion of this application. Teleconferences were held between the clinical review team and each consultant separately. During these teleconferences, each consultant expressed an opinion that, based upon the results of Studies C08-002, C08-003, and C09-001r, eculizumab appeared to provide a treatment benefit to patients. Each consultant also indicated that the risks of eculizumab treatment appeared to be acceptable for this patient population, given the life-threatening nature of the disease.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125166

Applicant: Alexion
Pharmaceuticals

Stamp Date: March 25, 2011

Drug Name:
eculizumab/SOLIRIS

NDA/BLA Type:sBLA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.			X	eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			PLR format submitted on April 5, 2011
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Tabular format only
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		ISE Module contains tabular summary of efficacy for individual studies
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Population PK/PD analysis performed from the following studies Study Number: C-08-002A <u>Study Title:</u> An Open-Label, Multi-Center Controlled Clinical Trial of Eculizumab in Adult Patients with Plasma Therapy-Resistant Atypical Hemolytic Uremic Syndrome (aHUS) Study Number: C-08-002B	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<u>Study Title:</u> An Open-Label, Multi-Center Controlled Clinical Trial of Eculizumab in Adult Patients with Plasma Therapy-Resistant Atypical Hemolytic Uremic Syndrome (aHUS) <u>Sample Size:</u> 17 adult and adolescent patients in C-08-002 A/B Study Number: C-08-003A <u>Study Title:</u> An Open-Label, Multi-Center Controlled Clinical Trial of Eculizumab in Adult Patients with Plasma Therapy-Sensitive Atypical Hemolytic Uremic Syndrome (aHUS) Study Number: C-08-003B <u>Study Title:</u> An Open-Label, Multi-Center Controlled Clinical Trial of Eculizumab in Adolescent Patients with Plasma Therapy-Sensitive Atypical Hemolytic Uremic Syndrome (aHUS) <u>Sample Size:</u> 20 adolescent and adult patients in C-08-003 A/B Study Number: C-09-001r <u>Study Title:</u> A Retrospective, Observational, Non-Interventional Trial to Assess Eculizumab Treatment Effect in Patients with Atypical Hemolytic Uremic Syndrome <u>Sample Size:</u> 20 patients provided samples for PK/PD <u>Location in submission:</u> module 5.3.4.2.1				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: c08-002A/B Indication: Plasma Therapy-Resistant Atypical HUS Pivotal Study #2 :c08-003A/B Indication: Plasma Therapy-Sensitive Atypical HUS Pivotal Study #3: C-09-001r Indication: Plasma Atypical HUS	X			Single Arm, open label studies acceptable for this rare disease because there are no approved therapeutic options
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			No formal agreement was made, but endpoints are consistent with Agency recommendations in pre-submission meetings: Primary endpoint of study C08-

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					002A/B: change in platelet count, but submission endpoints include complete hematologic response and complete TMA response; Primary endpoint of study C08-003A/B: TMA event-free status. Hematologic Normalization, Complete TMA response (hematologic normalization and improvement in renal function, defined as a $\geq 25\%$ decrease in serum creatinine from baseline). included as submission endpoints for both studies.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		No formal analysis; However, there are no approved therapies for aHUS. Population predominantly Caucasian
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Grading of AEs mild, moderate, not per CTCAE.
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?		X		The sponsor did not submit an analysis of QT interval, but ECG data is provided for Studies C08-002 and C08-003
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Provided a tabular listing of adverse event counts by organ class and PT in Post-marketing Database (From 17 Mar 2007 to 01 April 2010). AEs not graded. Provided summary of <i>N. meningitides</i> infections reported to date.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?		X		However, these guidelines apply to non-life threatening conditions; additionally, atypical HUS is a rare disease so accumulating data from a large number of patients is not feasible.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 11.0 was used to code verbatim terms to preferred terms
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Patient Summaries provided for all patients in Study C09-001r
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		No formal analysis; However, there are no approved therapies for aHUS. Population predominantly Caucasian

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			Study C08-002: CRFs for 17 patients submitted; CRFs for 23 patients submitted for Study C08-003; CRFs for 30 patients submitted for Study C09-001
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			All study reports contain the statement: "This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline"

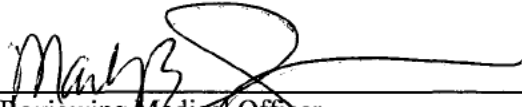
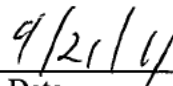
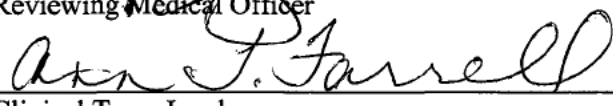
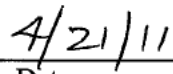
IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

 _____ Reviewing Medical Officer	 _____ Date
 _____ Clinical Team Leader	 _____ Date

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125166s172

CHEMISTRY REVIEW(S)



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

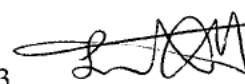
Office of Biotechnology Products
Division of Monoclonal Antibodies
29 Lincoln Dr., Bethesda, MD 20892
Tel. 301-827-0850

Memorandum of Review

Date: August 30, 2011

To: File for STN: 125166/172

From: Lixin Xu, M.D., Ph.D., Product Reviewer, HFD-123

 8/30/11

Through: Chana Fuchs, Ph.D., Team Leader, HFD-123

Patrick Swann, Ph.D., Deputy Division Director, HFD-123

 8/30/11
 8/30/11

Subject: Supplemental Biologic License Application (sBLA): to apply for the “treatment of atypical Hemolytic Uremic Syndrome (aHUS)” as a second indication for Soliris® (eculizumab).

Applicant: Alexion Pharmaceuticals Inc., 352 Knotter Drive, Cheshire, CT 06410

Product: Soliris® (eculizumab)

Submission Date: March 25, 2011

Received by Reviewer: March 25, 2011

Submission link: ([\\cbsap58\M\CTD_Submissions\STN125166\125166.enx](\\cbsap58\M\CTD_Submissions\STN125166\125166.enx))

Summary: BLA 125166 was approved on March 16, 2007 for PNH (Paroxysmal Nocturnal Hemoglobinuria). This supplement is a Supplemental Biologic License Application (sBLA) to apply for the “treatment of atypical Hemolytic Uremic Syndrome (aHUS)” as a second indication for Soliris® (eculizumab). This review covers the updated immunogenicity data for the proposed population and the environmental assessment section. Information provided in these sections are considered appropriate. Please refer below for detail.

Review of immunogenicity:

In the original BLA submission, the immunogenicity of Soliris was evaluated by a direct enzyme-linked immunosorbent assay (ELISA) using the Fab fragment of eculizumab as target for PNH indication. This resulted in a PMC (PMC#4) for developing a new assay: *To develop a validated and quantitative assay for the measurement of human anti-human antibodies (HAHA) for the detection of antibody formation to eculizumab. This assay will assess potential immune responses to the whole eculizumab molecule. Description of the validated assay will be submitted to the BLA as a CBE 30 by July 9, 2008.* Information regarding the new HAHA assay can be found in Submission STN 125166/31. This PMC was considered to be fulfilled by FDA on February 27, 2009. For the aHUS indication, the new assay, an electro-chemiluminescence (ECL) bridging assay using the whole molecular as target was used. In patients with aHUS treated with Soliris, antibodies to Soliris were detected in 1 of 37 (2.7%) by the ECL assay during the two clinical studies C08-002 A/B and C08-003 A/B. An ECL based neutralizing HAHA assay was also performed in all 37 patients with aHUS in the two clinical trials for detection of neutralizing antibodies. No neutralizing activity to Soliris was detected in patients with aHUS treated with Soliris. It should be noted that this neutralizing assay has poor sensitivity based on the validation data that was reviewed under Submission STN 125166/ (b) (4) for PMC#5 (*To develop a validated and sensitive assay for the measurement of neutralizing HAHA to eculizumab. Alternatively, Alexion commits to submit documentation to FDA demonstrating with due diligence that a suitable assay could not be feasibly developed and that the assessment of serum lactate dehydrogenase (LDH) is a sufficiently sensitive indicator of the presence of neutralizing antibodies. This information will be submitted to the BLA by July 9, 2008.*) This PMC was considered to be fulfilled by FDA on August 25, 2011.

According to the updated data of immunogenicity, the Section 6.2 Immunogenicity in the labeling has been updated as follow:

6.2 Immunogenicity -Original (for PNH population)

As with all proteins there is a potential for immunogenicity. Low titers of antibodies to Soliris were detected in 3/196 (2%) of all PNH patients treated with Soliris. No apparent correlation of antibody development to clinical response was observed. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Soliris in an enzyme linked immunosorbent assay (ELISA) and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to Soliris with the incidence of antibodies to other products may be misleading.

6.2 Immunogenicity -proposed language (for both PNH and aHUS populations)

As with all proteins there is a potential for immunogenicity. 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 molecular as target was used for the aHUS indication. Low titers of antibodies to Soliris were detected in 3/196 (2%) of all PNH patients treated with Soliris by the ELISA assay. In patients with aHUS treated with Soliris, antibodies to Soliris were detected in 1/37 (2.7%) by the ECL assay. An ECL based neutralizing HAHA assay with (b) (4) sensitivity was performed to detect neutralizing antibodies for the 37 patients with aHUS. No neutralizing activity to Soliris was detected in patients with aHUS treated with Soliris. No apparent correlation of antibody development to clinical response was observed in both indications. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Soliris in an ELISA based assay and/or an ECL based assay are highly dependent on the sensitivity and specificity of the assay used. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to Soliris with the incidence of antibodies to other products may be misleading.

Review of environmental assessment:

Environmental assessment section has been provided in the submission. In Section 1.12.14, the Sponsor requested a categorical exclusion from including an Environmental Assessment per 21CFR §25.15 and 21CFR §25.31. The Sponsor also calculated the Expected Introduction Concentration (EIC) according to FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application (July 1998). The estimated EIC according their calculation is (b) (4) µg/L, which is well below the categorical exclusion limit of 1.0 µg/L. It is considered adequate.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125166s172

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125166

Applicant: Alexion Pharmaceuticals **Stamp Date:** March 25, 2011

Drug Name: Eculizumab (SOLIRIS) **NDA/BLA Type:** Commercial

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	n/a		No pharmacology/toxicology data are submitted
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	n/a		No pharmacology/toxicology data are submitted
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	n/a		No pharmacology/toxicology data are submitted
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	n/a		No pharmacology/toxicology data are submitted
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	n/a		No pharmacology/toxicology data are submitted
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	n/a		No pharmacology/toxicology data are submitted
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	n/a		No pharmacology/toxicology data are submitted

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

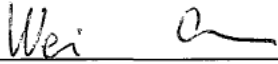
	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	*x		This will be a review issue
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	*x		This will be a review issue
11	Has the applicant addressed any abuse potential issues in the submission?	n/a		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	n/a		

* Issues generally identified during review.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Wei Chen, Ph.D		04/21/2011
Reviewing Pharmacologist		Date
Haleh Saber, Ph.D		04/21/2011
Team Leader/Supervisor		Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125166s172

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

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1. EXECUTIVE SUMMARY

This submission consists of the results of two prospective studies of C08-002 A/B and C08-003 A/B which are a single arm, multi-center clinical trial of eculizumab in adult/adolescent patients with plasma therapy (PT)-resistant and PT-sensitive atypical Hemolytic-Uremic Syndrome (aHUS), respectively, and one retrospective C09-001r study which is observational, non-interventional trial of aHUS patients who had received at least one eculizumab dose between 2007 and December 2009.

A dose of 600mg, 900mg, or 1,200mg was administered intravenously for induction period, week 5 and maintenance period, respectively, during the first 26 weeks treatment.

The primary objective for C08-002 A/B was to assess the effect of eculizumab to reduce Thrombotic microangiopathy (TMA) with the primary endpoint of platelet count change from baseline through week 26. The primary objective for C08-003 A/B was to assess the effect of eculizumab on TMA event-free status during the treatment period through the first 26 weeks. If the primary study objectives were met for C08-002 and C08-003, then the other primary objective for the two studies was to assess the number of patients who achieved a hematologic normalization from baseline through week 26 as well as to the data cutoff date. The objective of C09-001r was to assess safety and efficacy of eculizumab in aHUS patients treated outside of the applicant's sponsored clinical trial.

Two prospective studies, Study C08-002 and Study C08-003 observed efficacy results reasonably likely provide sufficient evidence for the clinical benefit in PT resistant and in PT-sensitive aHUS adult patients. For Study C09-001r, the efficacy results were similar to the two prospective studies through week 26 as well as through the end of the study. However, after week 26, large percent of patients dropped out of the study.

The key statistical issues and findings that impact them, with regards to the demonstration of efficacy are summarized as follows:

- These studies are single arm studies with very small sample sizes, 17 for C08-002, 20 for C08-003, and 30 for C09-001r. There may be limitations for the risk-benefit determination.
- For C09-001r study, 11 patients (36.7%) discontinued the study drug among 30 patients. Eleven patients (36.7%) were evaluated at week 26 and five patients (16.7%) were evaluated at week 52. Because of early dropouts, the long-term efficacy results may not be reliable.
- The applicant's inferential tests are not appropriate because these are single arm studies with very small sample sizes. P-values should not be included in the labeling.

Study results for two prospective studies:

- The platelet count normalization was over 80% for two prospective studies.
- Majority of patients (76.5% and 90% for C08-002 and C08-003, respectively) had hematologic normalization.

- The complete TMA responses were 15 out of 17 patients (88.2%) for C08-002, but only 5 out of 20 patients (25 %) for C08-003.
- The TMA event-free status was 15 out of 17 patients (88.2%) for C08-002 and 16 out of 20 patients (80%) for C08-003.
- The TMA intervention rates were decreased from before treatment of 0.88 to during treatment of 0 for C08-002 and from before treatment of 0.23 to during treatment of 0 for C08-003.

The efficacy results for two prospective studies are summarized in Table.

Efficacy Parameters	Study C08-002	Study C08-003
	N=17 n, (%)	N=20 n, (%)
Platelet Count Normalization	14 (82.4)	18 (90)
Hematologic Normalization	13 (76.5)	18 (90)
Complete TMA Response	11 (88.2)	5 (25)
TMA event-free status	15 (88.2)	16 (80)
TMA intervention rate		
Before treatment		
Median (range)	0.88 (0.04-1.59)	0.23 (0.05-1.09)
After Treatment		
Median (range)	0 (0-0.31)	0 (0)
eGFR improved by 15ml/min/1.73m ²	9 (52.9)	2 (10)

2. INTRODUCTION

2.1 Overview

Atypical hemolytic uremic syndrome (aHUS) is a rare, progressive, and life-threatening disease and is characterized as a thrombotic microangiopathic disease (TMA) which includes a triad of thrombotic thrombocytopenia, microangiopathic hemolytic anemia and impaired renal function. Alexion initiated two clinical trials to assess the safety and efficacy of eculizumab in patients with aHUS, which involved PT-resistant (C08-002A/B) and PT-sensitive patients (C08-003A/B); patients treated chronically with PT (chronic PT patients). In addition, data related to patient's aHUS history and eculizumab treatment were collected in a retrospective study of C09-001r which is outside of Alexion-sponsored clinical trial to assess the safety and efficacy.

The C08-002 and C08-003 trials were implemented via two study protocols, two for adult patients (C08-002A and C08-003A) and two for adolescent patients (C08-002B and C08-003B). The study C08-002A/B was designed to enroll patients with PT-resistant aHUS, defined as those aHUS patients where there is a persistence of biologic evidence of active TMA despite a

minimum of four PT sessions in the week prior to screening. In these patients, treatment with eculizumab was expected to suppress TMA, control hematological parameters, reduce hemolysis, and ultimately reverse the life-threatening acute kidney damage that can lead to end stage renal disease (ESRD) and thus improve overall renal function. The C08-003A/B study was designed to enroll patients with PT-sensitive aHUS, defined as those patients who were receiving chronic PT to manage the manifestations of ongoing chronic disease. Treatment with eculizumab in these patients was primarily aimed at controlling TMA by blocking the uncontrolled complement activation and consequences such as progressive renal damage and ongoing thrombotic thrombocytopenia without the need for burdensome PT.

A total of 17 patients (10 in Europe and 7 in US/Canada) were evaluated in the C08-002 A/B study, including one adolescent patient. A total of 20 patients (18 in Europe and 2 in US/Canada) were evaluated in the C08-003 A/B study, including five adolescent patients. A total of 30 patients were evaluated in the C09-00r study with a majority of pediatric or adolescent patients (15 patients (50%) <12 years, 4 patients (13%) adolescents and 11 patients (37%) adults).

The C09-001r trial was a systematic retrospective collection of data which was designed in August, 2009. The data for patients who were treated with eculizumab for aHUS between 2007 and December, 2009 were collected.

Table 1 : List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
C08-002 A/B	Phase 2	26 weeks	8 weeks	17	PT resistant aHUS
C08-003 A/B	Phase 2	26 weeks	8 weeks	20	PT sensitive aHUS
C09-001r	Retrospective study	26 weeks (patients who received at least 1 dose)		30	aHUS

Eculizumab 600 mg, 900 mg, or 1200 mg was administered intravenously according to the following regimens:

- Induction Period: patients received eculizumab 900mg via IV infusion over approximately 35 minutes once a week (every 7 ± 2 days) for 4 weeks.
- Week 5: patients received 1200 mg eculizumab via IV infusion over approximately 35 minutes for the 5th dose (7 ± 2 days after 4th dose).
- Maintenance Period: patients received eculizumab 1200mg via IV infusion over approximately 35 minutes every two weeks (every 14 ± 2 days).

If a patient administered plasmapheresis (PPH), plasma exchange (PE), or fresh frozen plasma (FFP), 600 mg eculizumab was to be administered (i) within 60 minutes after each PPH or PE, and (ii) within 60 minutes prior to each 2 units of FFP infusion, respectively.

2.2 Data Sources

The locations of the data are as follows;

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5.3.5 Atypical Hemolytic Uremic Syndrome

5.3.5.1 active-control-without-placebo

5.3.5.2 c09-001r

3. STATISTICAL EVALUATION

The review focuses on the efficacy results for eculizumab which is proposed for the indication in adults/adolescent patients with plasma therapy-resistant (C08-002A/B), plasma therapy-sensitive (C08-003 A/B) aHUS. The C09-001r trial was a systematic retrospective collection of data from the aHUS patients who were treated with eculizumab between 2007 and December, 2009.

3.1 Data and Analysis Quality

The quality and integrity of the submitted data were reviewed:

- The applicant didn't provide the derived datasets in the original submission. We could replicate the primary analysis datasets of two prospective studies after the applicant submitted the derived datasets as our requests.
- There was no derived datasets for the retrospective study.

3.2 Evaluation of Efficacy

3.2.1 Study C80-002 A/B

3.2.1.1 Study Design and Efficacy Endpoints

Study C08-002 A/B is a phase 2, single-arm, multi-center study to demonstrate the efficacy and safety of eculizumab in adults (≥ 18 years; C08-002 A) and adolescent patients (12- < 18 years with ≥ 40 kg; C08-002 B) with PT-resistant aHUS. The PT-resistant aHUS was defined as patients who did not respond or insufficiently responded to, or were intolerant to aggressive PT. AHUS patients with a persistence of biologic evidence of active TMA despite a minimum of 4 PT sessions in the week prior to screening were enrolled for the study. There were four periods of the study, the screening period, treatment period, extension treatment period and post-treatment period. Patients were to receive eculizumab 600mg, 900mg or 1200 mg intravenously according to the following regimen:

- Induction Period: eculizumab 900mg via IV infusion over approximately 35 minutes once a week (every 7 ± 2 days) for 4 weeks.
- Week 5: 1200 mg eculizumab via IV infusion over approximately 35 minutes for the 5th dose (7 ± 2 days after 4th dose).
- Maintenance Period: eculizumab 1200mg via IV infusion over approximately 35 minutes every two weeks (every 14 ± 2 days).

If PPH, PE, or FFP were administered, 600 mg eculizumab was to be administered (i) within 60 minutes after each PPH or PE, and (ii) within 60 minutes prior to each 2 units of FFP infusion, respectively.

After 26 weeks treatment of eculizumab, patients continued eculizumab treatment in the extension treatment period.

The primary endpoint was the platelet count change from baseline through week 26. If the result was statistically significant, then the other endpoint of the proportion of patients who achieve hematologic normalization from baseline through week 26 as well as through the data cutoff date was to be evaluated.

The secondary endpoints were:

- TMA intervention rate (# PT and # Dialysis [or New Dialysis] Events/Patient/Day) in the eculizumab treatment period (from baseline through week 26 and through the data cutoff date for PT and from the fifteenth day following the first eculizumab dose through week 26 and through the data cutoff date for new dialysis events) compared with the TMA intervention rate before the eculizumab treatment period (8 weeks before the treatment of eculizumab).
- TMA event-free status is defined as the absence for at least 12 weeks of (1) decrease in platelet count of $>25\%$ from the Platelet Count Pre-PT baseline Set-Point; (2) PT while the patient is receiving eculizumab, and (3) new dialysis.
- Quality of life measures
- Renal function measures
- Hemoglobin (at least 20 g/L)
- Complete TMA response
- Safety and tolerability
- Pharmacokinetic (PK) and pharmacodynamic (PD)

The laboratory tests were to be performed every week during the induction and every two weeks during the maintenance period in the treatment phase. Renal function measures, chronic kidney disease stage, and dialysis assessment were to be performed every month during the treatment phase. Post-treatment period assessments were to be performed at 1 week, 2 weeks, four weeks and 8 weeks after last dose of eculizumab.

The first patient was enrolled on June 9, 2009 and the last patient was enrolled on March 1, 2010. The data cutoff date was September 8, 2010.

Sample Size Determination

The planned sample size for the two protocols was at least 12 patients. This is based on a null hypothesis of no post-dose change from baseline in mean platelet count with approximately 88% power to detect as statistically significant improvement (mean change from baseline / standard deviation) of at least one when using a one sample t-test with a two-sided $\alpha = 0.05$. Up to approximately 15 patients were to be enrolled between the protocol of adult patients (C08-002A) and the protocol of adolescent patients (C08-002B).

3.2.1.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 17 patients were enrolled. All 17 enrolled patients were included in the intent-to treat (ITT) population. Among 17 ITT populations, four patients (24%) were off eculizumab at the time of the data cutoff date of September 8, 2010 and 13 (76%) patients continued into the extension treatment period with a minimum 2 months (8 weeks) follow-up. Two patients completed the 26-week treatment period, but did not continue in the extension period. The reasons for discontinuations are one patient due to adverse events 6 weeks from the first eculizumab dose and one patient due to a protocol violation. Among 17 patients, 5 did not meet the eligibility criteria.

Demographic and baseline characteristics based on 17 ITT populations are summarized in Table 2.

Table 2 : Patient Demographics: Study C08-002

	All Patients (N=17) n (%)
Age	
Median (Min, Max)	28 (17, 68)
Adults (≥ 18 Years)	16 (94.1)
Adolescent (12 to 17 years old)	1 (5.9)
Gender	
Female	12 (70.6)
Male	5 (29.4)
Race	
White	15 (88.2)
Other	2 (11.8)
Country	
US	7 (41.2)
Non-US	10 (58.8)
Any complement Regulatory Factor mutation or Auto-antibody Identified	
1 mutation	9 (52.9)
≥ 1 mutation	4 (23.5)
Type of Mutations	
Anti-Factor H antibody Titer (CFHR3-CFHR1)	1 (5.9)

C3	1 (5.9)
CD46 (MCP)	1 (5.9)
CFHR1, CFHR3, Anti-Factor H	1 (5.9)
Factor H	4 (23.5)
Factor H, CFHR1, CFHR3	1 (5.9)
Factor H, Factor I, CFHR3-CFHR1	1 (5.9)
Factor I	3 (17.6)

The median age was 28 years old. A total of 16 patients (94.1%) were older than 18 years. There were more female patients (70.6%) than male patients. Majority were White (88.2%). There were more Non-US patients (58.8%) than US patients. Thirteen patients (76.5%) had complement regulatory factor mutations or auto-antibodies identified, four of whom (23.5%) had multiple mutations.

Disease history is summarized in Table 3.

Table 3 : Disease History: Study C08-002

	All Patients (N=17)
Time from current exacerbation to screening (month)	
Median (Min, Max)	0.75 (0.23, 3.7)
Time from diagnosis to screening (month)	
Median (Min, Max)	9.7 (0.26, 236)
No. of patients with prior renal transplant	7 (41.2%)
First presentation of aHUS	7 (41.2%)

All patients initiated eculizumab treatment right after the aHUS exacerbation. The median months from the current aHUS exacerbation to screening was 0.75 months and the median months from diagnosis to screening was 9.7 months. Seven patients (41.2%) had a history of kidney transplant. There was no patient who had a history of nephrectomy. Seven patients (41.2%) were experiencing their first presentation of aHUS.

The patients' current aHUS exacerbation history is summarized in Table 4.

Table 4 : Patients' Current aHUS Exacerbation history: Study C08-002

	All patients (N=17)
No. PT session during Current Exacerbation	
Median (Min, Max)	17 (2, 37)
No. of PT sessions within 7 days prior to the 1 st dose	
Median (Min, Max)	6 (0, 7)
No. of patients with dialysis within 56 days of the 1 st dose	6 (35.3%)

All 17 patients received PT for an extended period of time for their aHUS exacerbation. Patients received median of 6 PT sessions in the 7 days prior to the first dose of eculizumab (All but one

patient had at least 4 PT sessions in the week prior to screening). One patient had to discontinue PT after 2 sessions because of intolerance to PT (allergic reaction) and had no PT in the 7 days prior to eculizumab. Six patients (35%) required dialysis within 56 days of the first dose of eculizumab.

The patients' baseline characteristics are summarized in Table 5.

Table 5 : Baseline Characteristics: Study C08-002

All patients (N=17)	
Platelet Count ($\times 10^9/L$)	
Median (Min, Max)	118 (62, 161)
$<150 \times 10^9/L$	15 (88.2%)
$\geq 150 \times 10^9/L$	2 (11.8%)
LDH (U/L)	
Median (Min, Max)	269 (134, 634)
$\leq$ URN	7 (41.2%)
$>$ URN	10 (58.8%)
Creatinine ($\mu\text{mol/L}$)	
Median (Min, Max)	256 (124, 787)
eGFR ($\text{mL}/\text{mkn}/1.73 \times \text{m}^2$) categories	
<15	7 (41.2%)
15-29	5 (29.4%)
30-44	4 (23.5%)
45-49	1 (5.9%)
CKD Stage	
3a	1 (5.9%)
3b	4 (23.5%)
4	5 (29.4%)
5	7 (41.2%)

Only two patients had a baseline platelet count of $\geq 150 \times 10^9/L$ at baseline, but their average platelet count was less than $150 \times 10^9/L$ at screening (within 3 days of treatment). Ten patients (58.8%) had elevated LDH at the time of the diagnosis of the current aHUS exacerbation with abnormal platelet count at entry. All patients had elevated creatinine with an eGFR less than $50 \text{ mL}/\text{min}/1.73 \times \text{m}^2$. The number of patients with Stage 4 or Stage 5 CKD was 12 patients (70.6%).

3.2.1.3 Statistical Methodologies

The ITT population was defined as all patients who received any amount of eculizumab, and were considered evaluable for safety and efficacy analyses. The first dose of eculizumab in the

Treatment Period was considered as study Day 0. The study day was presented and calculated relative to the first dosing day. No analyses were carried out for the per-protocol population that was defined in the final protocol.

For continuous variables, descriptive statistics (sample size (N), mean, standard deviation, median, minimum and maximum) were provided; for categorical variables, frequency counts and percentages were presented. All statistical tests were assessed at the two-sided 5% level. For all efficacy endpoints, the primary analysis was based on the ITT population, and missing data were imputed with last observation carried forward (LOCF) methods.

For the platelet count change from baseline to the first 26 weeks of treatment, a linear model (an ANOVA) was used with time and baseline platelet count as main effects and patient as a random effect. Repeated measurements made in time within each patient were modeled using an appropriate variance-covariance matrix structure such as compound symmetry (CS), Heterogeneous CS (CSH), Autoregressive (1) (AR(1)), Heterogeneous AR(1) (ARH(1)), Spatial Power (SP(POW)) and the unstructured (UN). The covariance structure resulting in lowest AIC was chosen for the final analysis. Change from baseline least squares (LS) means with corresponding 95% confidence intervals was presented at each time point. Statistical significance of a positive or negative increase in the change from baseline was assessed at the 5% level at each time point. The repeated measurement ANOVA on platelet count change from baseline was also performed using the LOCF method of imputation of missing values through Week 26.

For hematologic normalization was defined as normalization of both platelet count and LDH sustained for at least two consecutive measurements which spans a period of at least four weeks. Exact binomial 95% CIs were used for proportions. The maximum duration of hematological normalization excluded those patients who didn't achieve hematological normalization during the study.

3.2.1.4 Results and Conclusions

Primary Endpoints:

The primary efficacy endpoints were platelet count change from baseline and platelet count normalization. Change from baseline platelet count was calculated at each post-dose day of measurement (excluding Days 1 to 4) through Week 26 using a repeated measurement ANOVA model.

Applicant's primary endpoint results are summarized in Table 6.

Table 6 : Primary Endpoint of Change from Baseline in Platelet Count: Study C08-002

Time	N	Least Square Mean	95% CI
Week 1	17	42.2	(5.3, 79.0)
Week 26	15	72.7	(40.1, 105.2)

The change from baseline platelet count at each post-dose day of measurement demonstrated a significant increase in platelet count from week 1 through 26 weeks (except Day 21). The least square mean change from baseline through week 26 was $72.7 \times 10^9/L$ (95% CI: 40.1, 105.2).

The platelet count normalization was defined as the platelet count as $\geq 150 \times 10^9/L$ on at least two consecutive measurements for a period of at least four weeks. The proportion of patients who achieved a first normal platelet count from baseline through week 26 as well as through the data cutoff date is summarized in Table 7.

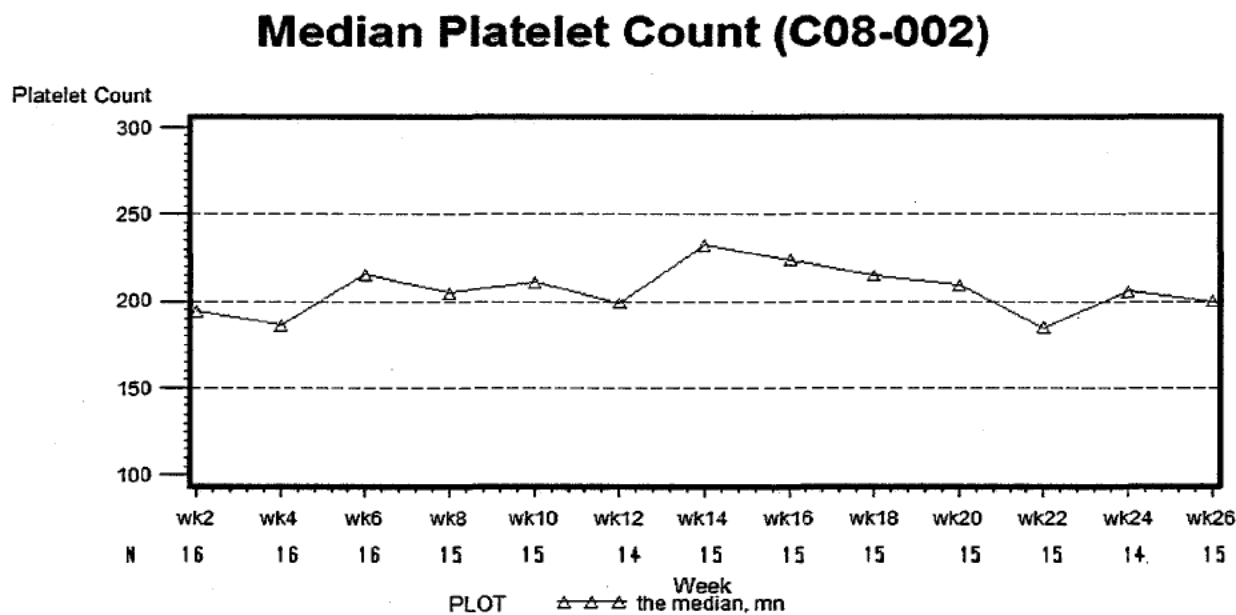
Table 7 : Platelet Count Normalization from Baseline to Week 26 as well as the Data Cutoff Date: Study C08-002

Baseline	$< 150 \times 10^9/L$ (N=15)	$\geq 150 \times 10^9/L$ (N=2)	Total
Normalization	13/15 (86.7%)	1/2 (50%)	14/17 (82.4%)

Total of 14 patients (82.4%) achieved the platelet count normalization, 13 out of 15 patients who had abnormal platelet count at baseline and one of two patients who had normal platelet count at baseline through week 26 as well as the data cutoff date.

The median platelet counts from week 2 through week 26 are plotted in Figure 1. This plot is median platelet counts overtime based on a decreasing number of subjects.

Figure 1 : Median Platelet Count (C08-002)



All median platelet counts were above $150 \times 10^9/L$ (N=2) from week 2 through week 26.

Reviewer's comment:

The reviewer plotted these median plots for platelet count, hemoglobin, haptoglobin, and LDH levels with median values overtime based on a decreasing number of subjects. Only for eGFR plot, the median change eGFR values from baseline were plotted overtime.

The other primary efficacy endpoint was the hematologic normalization (when the platelet count change from baseline was statistically significant). The hematologic normalization was defined as the normalization of platelet count and LDH improvement for at least two consecutive measurements for at least four weeks. The results of hematologic normalization are summarized in Table 8.

Table 8 : Hematologic Normalization from Baseline through Week 26 as well as the Data Cutoff Date: Study C08-002

	No complement mutation (N=4)	Positive for complement mutation (N=13)	Total N=17
No. of hematologic Normalization	3 (75%)	10 (76.9%)	13 (76.5%)
Maximum Duration of hematologic Week 26 (Days)			
Median (Min, Max)	154 (99, 154)	162 (42, 181)	154 (42, 181)
Data cutoff (Days)			
Median (Min, Max)	237 (196, 285)	263 (175, 431)	258 (175, 431)

Thirteen patients (76.5%) achieved a hematologic normalization (95% CI: (50, 93)) with 3 out of 4 no complement regular factor mutation patients (75%) and with 10 out of 13 positive for complement regular factor mutations or antibodies patients (76.9%) through week 26 as well as the data cutoff date. The median durations of hematologic normalization through week 26 and the data cutoff date were 154 and 258 days, respectively.

Reviewer's comment;

The duration of hematologic normalization for 13 patients who achieved a hematologic normalization was as follows;

	ID	Startday	Lastday	Cutoffday	MaxLength
1	2-198-001	14	189	168	175
2	2-197-001	28	224	154	196
3	2-045-002	1	211	181	210
4	2-141-001	13	238	169	225
5	2-196-001	28	265	154	237
6	2-029-001	19	264	163	245
7	2-045-001	22	280	160	258
8	2-070-001	72	339	110	267
9	2-041-001	83	368	99	285
10	2-040-001	134	436	48	302
11	2-039-001	140	449	42	309
12	2-110-001	112	448	70	336
13	2-191-001	3	434	179	431

Patients ID 2-197-001, 2-196,-001 and 2-041-001 had no complement mutation.

Secondary Endpoints:

TMA Intervention Rate

The difference in TMA intervention rates before treatment vs. eculizumab treatment period were calculated for each patient using a five-step algorithm. The five steps are as follows;

1. Counts of any PT events and all new dialysis events during the eculizumab treatment period (from the 1st dose of eculizumab to the earlier of last visit or 26 weeks after the 1st dose and last visit or date cutoff date) were added.
2. Step 1 value was divided by the total number of person-days from the same period to form the TMA intervention rate during eculizumab treatment.
3. Counts of all dialyses and any plasma therapies during the before eculizumab treatment period (the start of the current aHUS episode or 8 weeks prior to the 1st dose of eculizumab) were added.
4. Step 3 value was divided by the total number of person-days from this same period to form the pre-dose TMA intervention rate.
5. The difference in the before treatment period and during treatment period TMA intervention rates was formed.

The TMA intervention rate (# PT and # Dialysis Events/Patient/Day) in the eculizumab treatment period from baseline through week 26 and the data cutoff date were compared with the TMA intervention rate before treatment period. The results are summarized in Table 9.

Table 9 : Summary of TMA Intervention Rate through Week 26 and the Data Cutoff Date: Study C08-002

	Before treatment	During treatment
TMA Intervention Rate/Patient		
Mean (SD)	0.88 (0.4)	0.04 (0.1)
Median (Min, Max)	0.88 (0.04, 1.59)	0 (0, 0.31)
No. of patients with pre/new dialysis	6 (35.3%)	1 (5.9%)
No. of pre/new dialysis/patient		
Mean (SD)	3.2 (5.9)	0.8 (3.4)
Median (Min, Max)	0 (0, 17)	0 (0, 14)
No. of patients with any plasma therapies	17 (100%)	2 (11.8%)
No. of any plasma therapies/patient		
Mean (SD)	15.2 (9.0)	1.5 (4.9)
Median (Min, Max)	13 (2, 37)	0 (0, 20)
Person days in Period at week 26		
Mean (SD)	26.9 (19.1)	167.4 (41.6)
Median (Min, Max)	22 (6, 56)	182 (45, 182)
Person days in period at data cutoff		
Mean (SD)	26.9 (19.1)	273.0 (124.8)
Median (Min, Max)	22 (6, 56)	264 (45, 449)

In the before treatment period (8 weeks prior), all 17 patients had PT and 6 patients (35.3%) had dialysis. There were only three patients who required a TMA intervention (new dialysis and/or PT) after the start of treatment with eculizumab. The median TMA intervention rate was decreased from before treatment of 0.88 events/patient/day to during treatment of 0 events/patient/day.

TMA Event Free

TMA event-free status was defined as the absence for at least 12 weeks of [1] decrease in platelet count of >25% from the platelet count pre-PT baseline set-point; [2] PT while the patient is receiving eculizumab, and [3] new dialysis. Results for the analysis from baseline through week 26 as well as the data cutoff date are summarized in Table 10.

Table 10: TMA Event-Free and lengths of TMA Event-Free until Week 26 and the Data Cutoff Date: Study C08-002

	No complement Mutation (N=4)	Positive for complement mutation (N=14)	Total N=17
No. of TMA Free Status	3/4 (75%)	12 (70.6%)	15 (88.2%)
First Study Day of TMA Free (Days)			
Mean (SD)	84.0 (0)	92.1 (26.1)	90.5 (23.4)
Median (Min, Max)	84 (84, 84)	84 (84, 175)	84 (84, 175)
Length of TMA Free (Days) at Week 26			
Mean (SD)	179.7 (1.5)	171.7 (27.9)	172.8 (25.0)
Median (Min, Max)	180 (178, 181)	181 (84, 184)	181 (84, 184)
Length of TMA Free (Days) at Data Cutoff Date			
Mean (SD)	284.7 (74.2)	296.7 (120.6)	294.3 (110.6)
Median (Min, Max)	264 (223, 367)	271 (98, 448)	264 (98, 448)

A total of 15 among 17 eculizumab treated patients (88.2%:95% CI (64, 99)) achieved TMA event-free status including 3 patients without complement regulatory factor mutation and 12 patients with complement regulatory mutations. Duration of response was based on the longest interval in days between the time of the first TMA free date and the last response day or study day (week 26 or data cutoff date) in TMA event-free status patients, the median durations were 181 days at week 26 and 264 days at data cutoff date.

Reviewer's comment: Patients who achieved TMA-free events were listed their first day of TMA-free events achieved and the lengths of TMA free.

Obs	PATID	1 st _day_tma_free	length_tma_free
1	2-205-001	175	98
2	2-198-002	87	187
3	2-198-001	84	188
4	2-045-002	84	210
5	2-197-001	84	223
6	2-141-001	84	237

7	2-029-001	84	263
8	2-196-001	84	264
9	2-045-001	84	279
10	2-070-001	84	338
11	2-041-001	84	367
12	2-040-001	87	432
13	2-191-001	84	433
14	2-110-001	84	447
15	2-039-001	84	448

Patients ID 2-197-001, 2-196,-001 and 2-041-001 had no complement mutation.

Change in renal function

Changes in renal function parameters from baseline through week 26 and the data cutoff date were assessed by examining the following: (1) change in CKD Stage (at least one CKD stage), (2) change from baseline in eGFR (at least 15 mL/min/1.73 m² improvement) and (3) proportion of patients whose creatinine decreased at least 25% from baseline. Improvement of eGFR $\geq$ 15 mL/min/1.73m², improvement of at least one CKD stage, or decrease of creatinine $\leq$ 25% decrease from baseline maintained at least two scheduled measurements for at least 4 weeks from baseline through week 26 are summarized in Table 11.

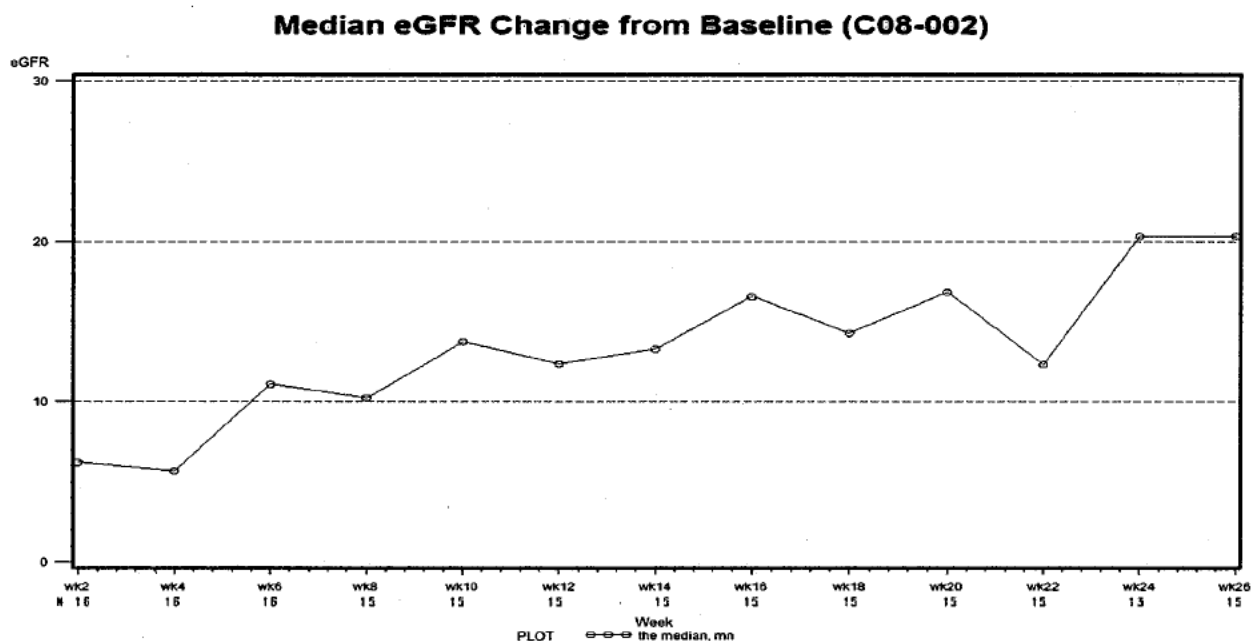
Table 11: Changes in Renal Function Parameters from Baseline through Week 26 and the Data Cutoff Date: Study C08-002

	No complement Mutation (N=4)	Positive for complement mutation (N=13)	Total N=17
eGFR improvement at least 4 weeks at week 26			
$\geq$ 15 mL/min/1.73m ²	1/4 (25%)	7/13 (53.8%)	8/17 (47.1%)
eGFR improvement at least 4 weeks at data cutoff date			
$\geq$ 15 mL/min/1.73m ²	2/4 (50%)	7/13 (53.8%)	9/17 (52.9%)
CKD Stage improvement at least 4 weeks until week 26 and data cutoff date			
$\geq$ one stage	2/4 (50%)	8/13 (61.5%)	10/17 (58.5%)
Creatinine decrease at least 4 weeks until week 26 and data cutoff date			
$\leq$ 25% decrease from Baseline	2/4 (50%)	9/13 (69.2%)	11/17 (64.7%)

Eight (47.1%; 95% CI: (23, 72)) and 9 patients (52.9%; 95% CI: (28, 77)) out of 17 patients maintained at least two scheduled measurements of eGFR $\geq$ 15 mL/min/1.73 m² for at least 4 weeks until week 26 and until the data cutoff date from baseline levels, respectively. Ten of 17 patients (59%; 95% CI: (33, 82)) maintained improvement in CKD stage of one stage for at least 4 weeks through week 26 as well as the data cutoff date from baseline stage. Eleven out of 17 patients (64.7%; 95% CI (38, 86)) maintained creatinine decrease $\geq$ 25% from baseline at least 4 weeks through week 26 as well as the data cutoff date compared to baseline levels. There was no difference in achieving maintained improvements of renal function parameters between patients with or without identified complement regulatory factor mutation or auto-antibody.

The median eGFR changes from baseline are plotted in Figure 2.

Figure 2 : Median eGFR Change from Baseline (C08-002)



The median of eGFR change from baseline was increased from below 10 mL/min/1.73 m² at week 2 to 20 mL/min/1.73 m² at week 26.

Complete TMA Response

Complete TMA response was defined as hematologic normalization plus improvement in renal function (25% reduction from baseline in serum creatinine maintained for two consecutive measurements for at least 4 weeks). The results of complete TMA response from baseline through week 26 well as the data cutoff date are summarized in Table 12.

Table 12: Complete TMA Response from Baseline through Week 26 and the Data Cutoff Date: Study C08-002

	No complement mutation (N=4)	Any complement Mutation (N=13)	Total N=17
Complete TMA response			
No. of patients	2 (50%)	9 (69.2%)	11 (64.7%)
Duration of TMA response from baseline to week 26 (Days)			
Mean (SD)	126.5 (38.9)	118.6 (52.8)	120.0 (48.9)
Median (Min, Max)	127 (99, 154)	137 (42, 169)	137 (42, 169)
Duration of TMA response from baseline to data cutoff date (Days)			
Mean (SD)	261 (33.9)	278.4 (63.5)	275.3 (58.2)
Median (Min, Max)	261 (237, 285)	267 (175, 389)	267 (175, 389)

The complete TMA response was observed in 11 out of 17 patients (64.7%; 95% CI: (38, 96)) from baseline through week 26 and the data cutoff date. The median durations of complete TMA response were 137 days and 267 days from baseline through week 26 and the data cutoff date, respectively.

Change in Hemoglobin

The patients whose hemoglobin improved at least ≥ 20 g/L from baseline through week 26 as well as the data cutoff date are summarized in Table 13.

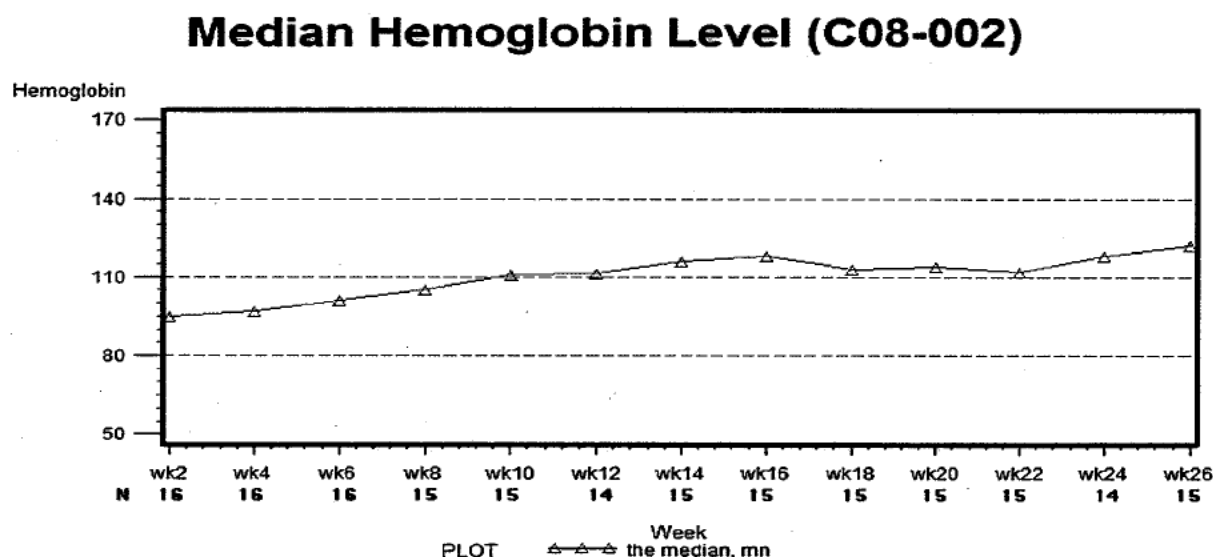
Table 13: Change from Baseline Hemoglobin through Week 26 as well as the Data Cutoff Date: Study C08-002

	No complement mutation (N=4)	Any complement Mutation (N=13)	Total N=17
≥ 20 g/L for ≥ 4 wks until week 26			
No. of Patients	2/4 (50%)	9/13 (69.2%)	11/17 (64.7%)
≥ 20 g/L for ≥ 4 wks until data cutoff date			
No. of patients	2/4 (50%)	10/13 (76.9%)	12/17 (70.6%)

A total of 11 patients (64.7%; 95% CI: (38, 86)) and 12 patients (70.6%; 95% CI: (44, 90)) until week 26 and the data cutoff date, respectively, maintained the improvement in hemoglobin ≥ 20 g/L for at least 4 weeks from baseline. There was no difference in maintained hemoglobin improvement between patients' with or without identified complement regulatory factor mutations or auto-antibodies.

The median hemoglobin levels from week 2 through week 26 are plotted in Figure 3.

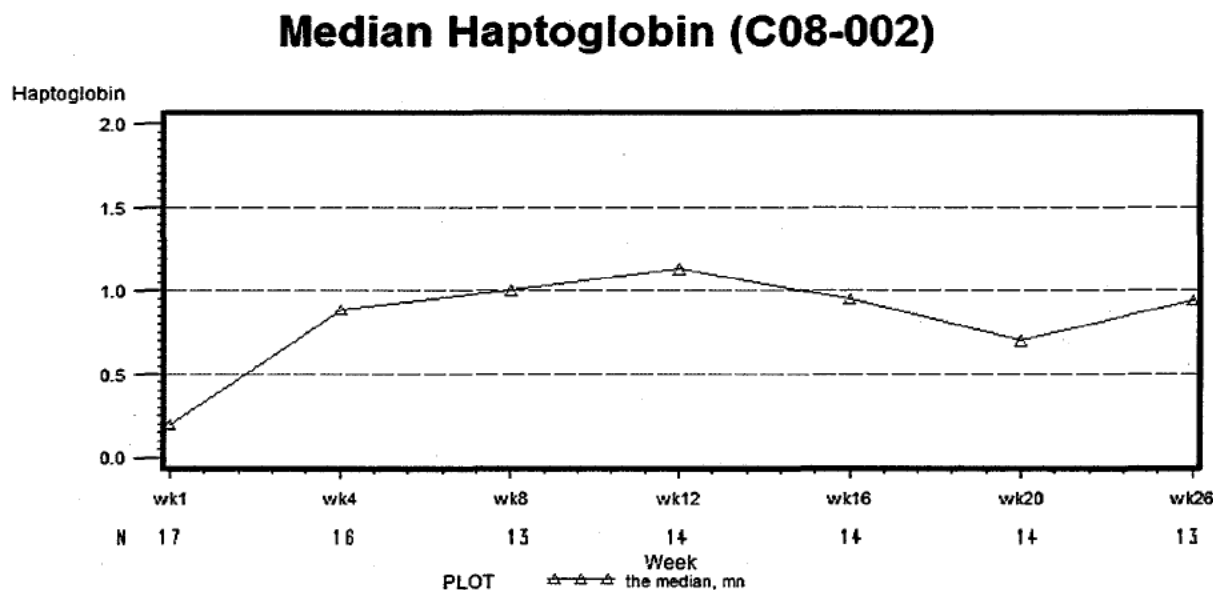
Figure 3 : Median Hemoglobin Levels (C08-002)



The median hemoglobin levels were increased from 95 g/L at week 2 to above 120 g/L at week 26.

The median haptoglobin levels are plotted in Figure 4.

Figure 4 : Median Haptoglobin Levels (C08-002)



The median haptoglobin was 0.2 g/L at week 1, 0.88 g/L at week 4, above 1 g/L from week 8 to up to week 12, but decreased below 1 g/L from week 16 to week 26.

LDH

The patient's LDH levels below the upper limit of its normal range from baseline through week 26 as well as the data cutoff date are summarized in Table 14.

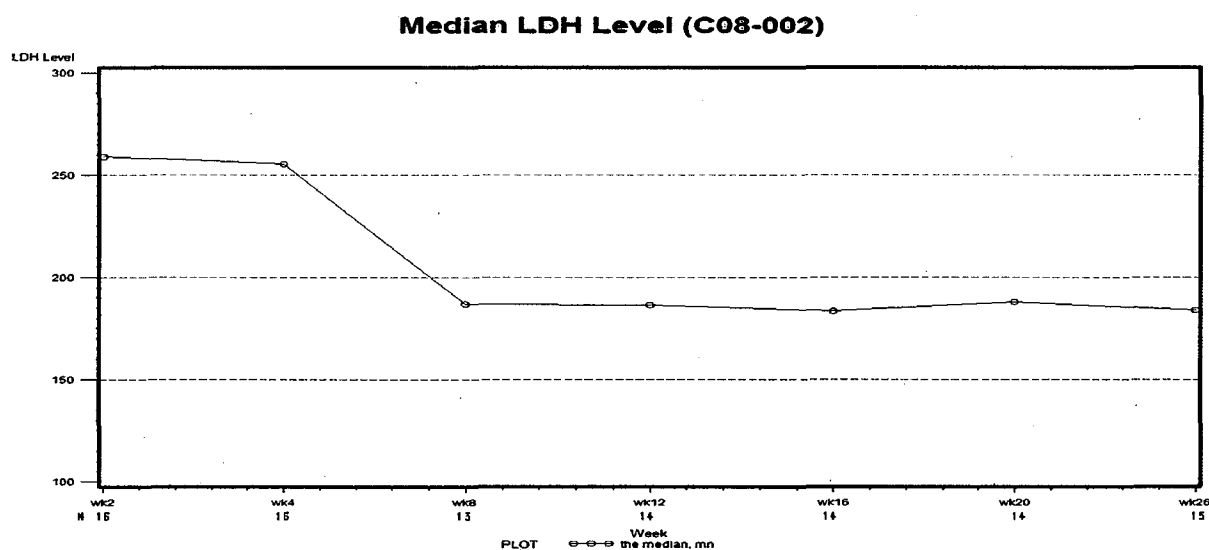
Table 14: LDH Levels from Baseline through Week 26 and the Data Cutoff Date: Study C08-002

	No complement Mutation (N=4)	Any complement Mutation (N=13)	Total N=17
LDH <URN at least 2 wks for ≥4 wks from baseline until week 26 and data cutoff date			
No. of patients	3/4 (75%)	11/13 (84.6%)	14/17 (82.4%)

Fourteen of 17 patients (82.4%; 95%CI: (57, 96)) maintained improvement (two consecutive visits for at least 4 weeks) with a decreased LDH levels below the ULN from baseline to week 26 as well as the data cutoff date. Similar results were observed with or without complement regulatory factor mutations.

The median LDH levels are plotted in Figure 5.

Figure 5 : Median LDH Levels (C08-002)



The median LDH (U/L) levels were decreased from week 8 and stayed 180 U/L until week 26.

Efficacy Conclusions for Study C08-002

- The change from baseline platelet count at each post-dose day of measurement significantly increased in platelet count from week 1 through 26 weeks (except Day 21). The least square mean change from baseline through week 26 was $72.7 \times 10^9/L$ (95% CI: 40.1, 105.2).
- Fourteen of 17 patients (82.4%) achieved the platelet count normalization including 13 of 15 patients (86.7%) with an abnormal baseline value.
- Thirteen patients (76.5%) achieved a hematologic normalization (95% CI: (50, 93)) through week 26 as well as the data cutoff date. The median durations of hematologic normalization through week 26 and the data cutoff date were 154 and 258 days, respectively.
- In the before treatment period (8 weeks prior), all 17 patients had PT and 6 patients (35.3%) had dialysis. During the treatment, three patients were required a TMA intervention (new dialysis and/or PT). The median TMA intervention rate was decreased from before treatment of 0.88 events/patient/day to during treatment of 0 events/patient/day.
- Fifteen out of 17 patients (88.2%; 95% CI (64, 99)) achieved TMA event-free status from baseline through week 26 and the data cutoff date. The median durations of TMA event-free were 181 days at week 26 and 264 days at the data cutoff date, respectively.
- In the change in renal function, 8 (47.1%; 95% CI: (23, 72)) and 9 patients (52.9%; 95% CI: (28, 77)) out of 17 patients maintained at least two scheduled measurements of eGFR $\geq 15 \text{ mL/min/1.73 m}^2$ for at least 4 weeks until week 26 and until the data cutoff date from baseline levels, respectively. Ten of 17 patients (59%; 95% CI: (33, 82)) maintained

improvement in at least one CKD stage for at least 4 weeks through week 26 as well as the data cutoff date from baseline stage. Eleven out of 17 patients (64.7%; 95% CI (38, 86)) maintained creatinine decrease $\geq$ 25% from baseline for at least 4 weeks through week 26 as well as the data cutoff date from baseline levels.

- The complete TMA response was observed in 11 out of 17 patients (64.7%; 95% CI: (38, 96)) from baseline through week 26 and the data cutoff date. The median durations of complete TMA response were 137 days and 267 days from baseline through week 26 and the data cutoff date, respectively.
- Fourteen of 17 patients (82.4%; 95% CI: (57, 96)) maintained improvement (two consecutive visits for at least 4 weeks) with a decreased LDH levels below the ULN from baseline to week 26 as well as the data cutoff date.
- Complement regulatory factor mutation status did not have a significant effect on the response to eculizumab, as high response rates were observed for patients achieving TMA event-free status, normalization of platelet count, hematologic normalization and complete TMA response. For renal function parameters, responders with complement regulatory factor mutations showed a slightly higher probability of hemoglobin improvement.

3.2.2 Study C08-003 A/B

3.2.2.1 Study Design and Endpoints

Study C08-003 A/B is a phase 2, single arm, multi-center, controlled trial of eculizumab in adults ($\geq$ 18 years in the protocol C08-003A) and adolescent (12-18 with $\geq$ 40 kg in the protocol C08-003B) with aHUS receiving chronic PT. Study C08-003 was designed to enroll patients with PT-sensitive aHUS, defined as those patients who were receiving chronic PT to manage the manifestations of ongoing chronic disease. There were 5 stages in the study, the screening period (visit 1), the observation period (visit 2), the treatment period, the extension treatment period, and the post-treatment period. The dosage for eculizumab was the same as that of the study C08-002.

If the primary efficacy endpoint of the TMA event-free status from baseline to week 26 was statistically significant, an additional efficacy primary endpoint of hematologic normalization was to be evaluated. There was no adjustment for multiple comparisons.

The secondary endpoints were:

- Evaluate additional efficacy endpoints during the treatment period to the first 26 weeks as well as to the data cutoff date, such as the effect of eculizumab on:
 - TMA intervention rate at the end of the first 26 weeks of the treatment period compared with the TMA intervention rate during the observation period to the first eculizumab dose
 - Reduction of TMA as indicated by thrombocytopenia and measured by platelet count change from baseline during the first 26 weeks of the treatment period

- Quality of life measures
- Renal function measures
- Hemoglobin levels
- LDH response
- Complete TMA response (analysis requested by the regulatory authorities)
- Safety and tolerability
- Pharmacokinetics (PK) and pharmacodynamics (PD) properties
- Exploratory efficacy analyses on the following by using the available data from the pre-eculizumab treatment and eculizumab treatment periods to quantify differences once patients begin treatment with eculizumab:
 - Plasma therapy frequency
 - Platelet count measures
 - LDH
 - eGFR
 - Hemoglobin
 - Creatinine

Determination of Sample size

The sample size of 20 patients was planned between the protocols of adults and adolescent patients. This is based on a true expected probability of TMA event-free eculizumab treated patient of 40%, then the statistical power to detect a statistically significant difference from a minimum probability ($H_0: P=P_{\min}$ vs. $P>P_{\min}$) is approximately 93.5% when $P_{\min}=10\%$, 80.8% when $P_{\min}=15\%$, and 61.0% when $P_{\min}=20\%$.

3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 23 patients were enrolled. Among 23 enrolled patients, 20 patients received at least one dose of eculizumab which were included in the intent-to treat (ITT) population. Among 20 ITT populations, only one patient was off eculizumab in the extension period after completing maintenance phase. Four out of 20 patients did not meet eligibility criteria.

Patient demographic and baseline characteristics based on 20 ITT populations are summarized in Table 15.

Table 15: Patient Demographic and Baseline Characteristics: Study C03-008

	ITT population (N=20) n, (%)
Age	
Median (Min, Max)	28 (13, 63)
Adolescent (12 to <18)	5 (25)
Adults (≥ 18)	15 (75)
Gender	
Female	12 (60)

Male	8 (40)
Mutation or Auto-Antibody identified	14 (70)
One mutation	8 (40)
Multiple mutation	6 (30)
Type of mutation	
Anti-factor H antibody-Qualitative	1 (5)
CD46 (MCP)-Mutation	1 (5)
CD46 (MCP)-Mutation, Factor I-Mutation	1 (5)
CFHR1, CFHR3-Mutations	1 (5)
CFHR3-CFHR1, CFHR3-Mutations, Anti-Factor H antibody-Qualitative	1 (5)
Factor B-Mutation	1 (5)
Factor H-Mutation	1 (5)
Factor H, C3-Mutations	1 (5)
Factor H, CFHR1, CFHR3-Mutation	1 (5)
Factor I-Mutation	2 (10)
Factor I, C3-Mutations	1 (5)

The median age was 28 years old with 5 adolescent and 15 adult patients. There were 12 female and 8 male patients. Fourteen patients had an identified complement regulatory factor mutation, and 6 patients had multiple mutations. Only one patient had a mutation resulting in production of CFH-specific antibodies. The most common mutations were in complement Factor H (3 patients) and Factor I (2 patients).

Patients' aHUS and aHUS exacerbation history are summarized in Table 16.

Table 16: aHUS Exacerbation History: Study C08-003

ITT Population (N=20)	
Time from aHUS diagnosis to screening (Months)	
Mean (SD)	87 (87)
Median (Min, Max)	48 (0.66, 286)
Kidney transplant	8 (40)
First present of aHUS	5 (25)
Time from current exacerbation to screening (Months)	
Mean (SD)	14 (13)
Median (Min, Max)	8.6 (1.2, 45)
Number of PT sessions during current exacerbation	
Mean (SD)	83 (53)
Median (Min, Max)	62 (20, 230)
Number of PT sessions within 7 days prior to the first dose	
Mean (SD)	1.6 (0.68)
Median (Min, Max)	1.5 (1, 3)
Dialysis within 56 days of the first dose	2 (10)

Median time from first diagnosis to screening was 48 months. Eight patients (40%) had at least one kidney transplant. The median time that patient experienced an aHUS exacerbation prior to screening was 8.6 months. The median number of PT sessions within 7 days prior to the first dose of eculizumab was 1.5. Only two patients were on going dialysis.

Baseline laboratory values are summarized in Table 17.

Table 17: Baseline Laboratory Values: Study C08-003

	All Patients (N=20)
Platelet Count ($\times 10^9/L$)	
Mean (SD)	228 (78)
Median (Min, Max)	218 (105, 421)
< 150 $\times 10^9/L$	3 (15)
$\geq 150 \times 10^9/L$	17 (85)
LDH (U/L)	
Mean (SD)	223 (70)
Median (Min, Max)	200 (151, 391)
$\leq$ ULN	16 (80)
$>$ ULN	4 (20)
Creatinine ($\mu\text{mol/L}$)	
Mean (SD)	287 (215)
Median (Min, Max)	234 (106, 893)
eGFR ($\text{mL}/\text{min}/1.73\text{m}^2$)	
<15	4 (20)
15-29	6 (30)
30-44	6 (30)
45-59	2 (10)
60-89	2 (10)
CKD Stage	
Stage 1	0
Stage 2	2 (10)
Stage 3a	2 (10)
Stage 3b	6 (30)
Stage 4	6 (30)
Stage 5	4 (20)

The majority of patients had platelet count $\geq 150 \times 10^9/L$ (17 patients) and normal LDH (16 patients) at baseline. Ten patients had CKD Stage 4 or 5 and two patients had chronic dialysis.

3.2.2.3 Statistical Methodologies

The point estimates and exact 95% confidence intervals (CIs) for the proportions of attaining a TMA event-free status and hematologic normalization from baseline through week 26 as well as through the data cutoff date, were calculated. These proportions were calculated for patients with and without identified complement regulatory factor mutation or auto-antibodies.

If the McNemar's test involving the protocol specified primary endpoint of TMA event-free status from baseline to week 26 was statistically significant, then an additional efficacy primary endpoint of agency requested hematologic normalization was to be evaluated. There was no adjustment for multiple comparisons.

TMA intervention rate was evaluated by calculating the difference in the TMA intervention rates for the before eculizumab treatment period versus during the eculizumab treatment period and a signed rank test (two-sided) was assessed for the differences.

Platelet count change from baseline at each post-dose day of measurement (excluding Days 1 to 4) through the first 26 weeks of treatment was assessed using a repeated measurement ANOVA model. Statistical significance of a positive or negative increase in the change from baseline was assessed at the 5% level at each time point.

Changes from baseline of the renal function parameters CKD stage, eGFR, and creatinine were summarized. Counts and proportions reflecting changes in these parameters were also presented. Frequency counts, proportions, and exact 95% CIs for patients whose hemoglobin improved at least 20 g/L from baseline and whose LDH was within normal range (<ULN) were tabulated. The proportion of patients who achieved a complete TMA response from baseline through week 26 as well as through the data cutoff date was calculated and exact binomial CIs were used.

3.2.2.4 Results and Conclusions

Primary Endpoints:

The primary endpoint of TMA event-free status which was defined as the absence for at least 12 weeks of 1) decrease in platelet count of > 25% from the platelet count pre-PT baseline set-point; 2) PT while the patient is receiving eculizumab, and 3) new dialysis. The results of TMA event-free status from baseline through week 26 as well as the data cutoff date are summarized in Table 18.

Table 18: Summary of TMA Event-Free Status through Week 26 and the Data Cutoff Date: Study C08-003

	No complement Mutation (N=6)	Positive for complement mutation (N=14)	Total N=20
No. of TMA Free Status	4/6 (66.7%)	12 (70.6%)	16 (80%)
First Study Day of TMA Free (Days)			
Mean (SD)	84.0 (0)	88.6 (15.9)	87.4 (13.8)
Median (Min, Max)	84 (84, 84)	84 (84, 139)	84 (84, 139)
Length of TMA Free (Days) at Week 26			
Mean (SD)	181.8 (0.96)	176.2 (15.9)	177.6 (13.8)
Median (Min, Max)	182 (181, 183)	181 (126, 182)	181 (126, 183)
Length of TMA Free (Days) at Data Cutoff Date			
Mean (SD)	254.5 (79.6)	275.3 (66.6)	270.1 (67.9)
Median (Min, Max)	237 (182, 362)	301 (126, 358)	280 (126, 362)

Sixteen out of 20 patients (80%; 95% CI (56, 94)) achieved the primary endpoint of TMA event-free status through week 26 as well as the data cutoff date. The median duration of the start day of the TMA event-free status was 84 days. The median duration of TMA event-free status through week 26 and the cutoff date were 181 and 280 days, respectively.

Hematologic Normalization

Hematologic normalization was defined as normalization of platelet count and LDH sustained for at least two consecutive measurements within a period of at least 4 weeks. The results for the hematologic normalization from baseline to week 26 as well as the data cutoff date are summarized in Table 19.

Table 19: Hematologic Normalization from Baseline to Week 26 and the Data Cutoff Date: Study C08-003

	No complement mutation (N=6)	Positive for complement mutation (N=14)	Total N=20
Hematologic Normalization			
No. of Patients	5 (75%)	13 (76.9%)	18 (90%)
Maximum Duration of hematologic at week 26 (Days)			
Mean (SD)	168.8 (24.1)	174.5 (9.1)	172.9 (14.2)
Median (Min, Max)	181 (126, 181)	181 (154, 181)	181 (126, 181)
Maximum Duration of hematologic at data cutoff date (Days)			
Mean (SD)	233.4 (83.2)	275.8 (51.4)	264.0 (62.2)
Median (Min, Max)	203 (154, 363)	294 (181, 336)	267 (154, 363)

Eighteen out of 20 patients (90%; 95% CI: (68, 99)) achieved a hematologic normalization from baseline through week 26 as well as the data cutoff date and maintained the normal platelet count after discontinuation of PT and start of eculizumab therapy.

Reviewer's comments:

One patient who had baseline platelet count of $<150 \times 10^9/L$ increased to $\geq 150 \times 10^9/L$ after 7 days later and had at least 2 consecutive platelet count measurements $\geq 150 \times 10^9/L$ for at least 4 weeks period after 42 days later. Other 17 patients who had $\geq 150 \times 10^9/L$ at baseline had at least 2 consecutive platelet count measurements $\geq 150 \times 10^9/L$ for at least 4 weeks period after 28 days later.

Secondary Endpoints:

TMA intervention rate

The estimated TMA intervention rates (number of PT sessions plus dialysis/patient/day) before eculizumab treatment (during the Observation Period) and during treatment are summarized in Table 20.

Table 20: Summary of TMA Intervention Rate through Week 26 and the Data Cutoff Date: Study C08-003

	Before treatment	During treatment
TMA Intervention Rate/Patient		
Mean (SD)	0.29 (0.26)	0
Median (Min, Max)	0.23 (0.05, 1.09)	0
No. of patients with pre/new dialysis	2 (10%)	0
No. of pre/new dialysis/patient		
Mean (SD)	4 (13.4)	0
Median (Min, Max)	0 (0, 56)	0
No. of patients with any plasma therapies	20 (100%)	20 (100%)
No. of any plasma therapies/patient		
Mean (SD)	12.3 (7.0)	0
Median (Min, Max)	10 (3, 25)	0
Person days in Period 26 weeks		
Mean (SD)	55.8 (0.6)	182 (0)
Median (Min, Max)	56 (54, 57)	182 (182, 182)
Person days in Period Data Cutoff Date		
Mean (SD)	55.8 (0.6)	279.4 (62.2)
Median (Min, Max)	56 (54, 57)	282 (182, 364)

In the before treatment period (8 weeks prior), only 2 patients had dialysis. There was no patient who required a TMA intervention (new dialysis and/or PT) after the start of treatment with eculizumab. The median TMA intervention rate was decreased from 0.23 events/patient/day to 0 events/patient/day. For the eculizumab treatment period, the results of the TMA intervention rates from baseline through week 26 and from baseline through the data cutoff date were identical. The median person days in period 26 weeks and in period data cutoff date were 182 and 282 days, respectively.

Platelet Count Change from Baseline

Platelet count change from baseline was analyzed at each on-treatment day of measurement (excluding days 1 through 4) through week 26 as well as the data cutoff date using a repeated measure ANOVA model. The results are summarized in Table 21.

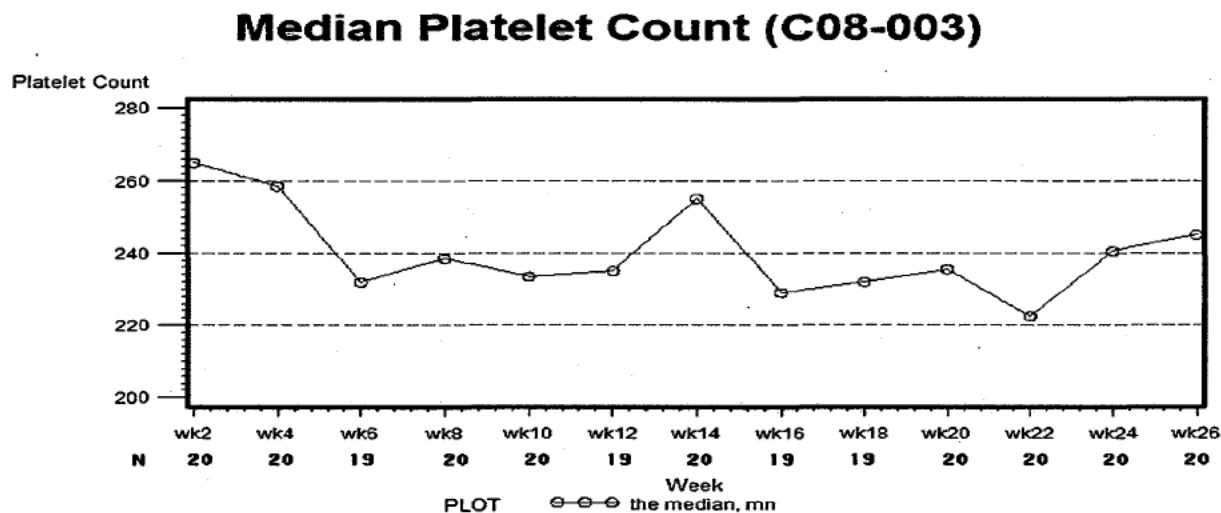
Table 21: Change from Baseline in Platelet Count through Week 26: Study C08-003

Time	N	Least Square Mean	95% CI
Week 1	19	22.2	(-0.8, 45.1)
Week 2	20	32.2	(9.4, 54.9)
Week 3	20	32.1	(9.3, 54.8)
Week 4	20	20.9	(-1.9, 42.6)
Week 26	20	5.3	(-17.5, 28.0)

The change from baseline platelet count at each post-dose day of measurement demonstrated a significant increase in platelet count from week 2 and week 3. The least square mean change from baseline through 26 weeks was $5.3 \times 10^9/L$ (95% CI: -17.5, 28.0). There was no difference in platelet count change from baseline from week 4 through week 26 including week 1.

The median platelet counts are plotted in Figure 6.

Figure 6 : Median Platelet Counts (C08-003)



The median platelet counts were over $220 \times 10^9/L$ from week 2 through week 26.

Platelet Count Normalization

The platelet count normalization was defined as the platelet count as $\geq 150 \times 10^9/L$ on at least two consecutive measurements for a period of at least four weeks. The proportion of patients

achieved the first normal platelet count from baseline through week 26 as well as through the data cutoff date is summarized in Table 22.

Table 22: Platelet Count Normalization from Baseline to Week 26 as well as the Data Cutoff Date: Study C08-003

Baseline	<150 x10 ⁹ /L (N=3)	≥ 150 x10 ⁹ /L (N=17)	Total (N=20)
Normalization	1/3 (33.3%)	17/17 (100%)	18/20 (90%)

A total of 18 patients (90%) achieved the platelet count normalization, one out of three patients who had abnormal platelet count at baseline and all 17 patients who had normal platelet count at baseline through week 26 as well as the data cutoff date.

LDH

The patients whose LDH level below the upper limit of its normal range from baseline through week 26 as well as through the data cutoff date is summarized in Table 23.

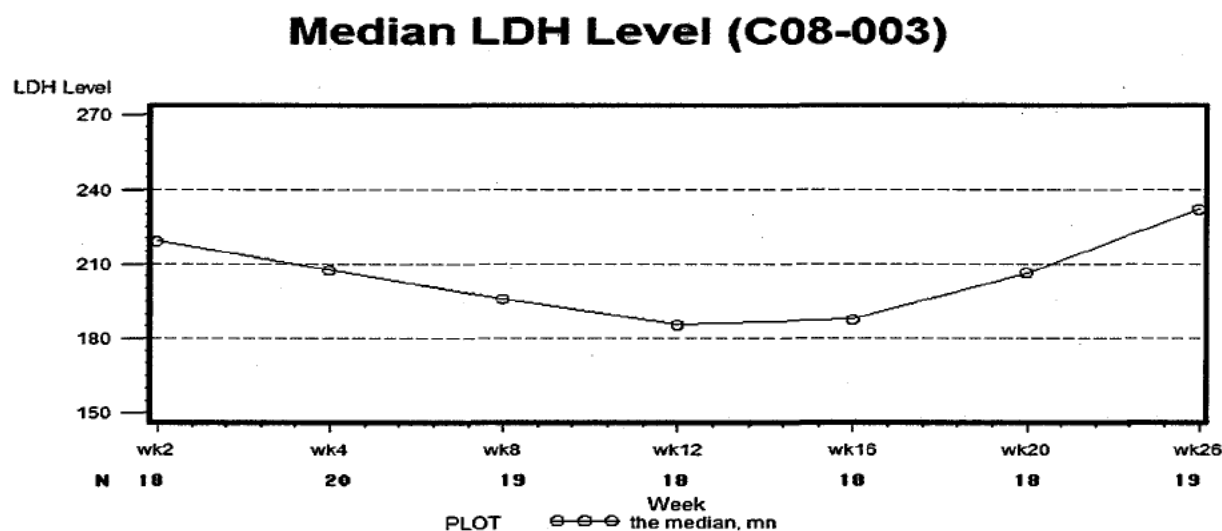
Table 23: LDH Level below URN from Baseline to Week 26 and the Data Cutoff Date: Study C08-003

	No complement Mutation (N=6)	Any complement Mutation (N=14)	Total N=20
LDH <URN at least 2 wks for ≥4 wks			
No. of patients	6 (100%)	13/14 (92%)	19/20 (95%)

A total of 19 out of 20 patients (95%; 95% CI: (76, 100)) maintained the decrease in LDH levels below URN from baseline through week 26 as well as the data cutoff date. There were no differences in the proportion of patients with an identified complement regulatory factor mutation or auto-antibody compared to those without complement regulatory factor mutation.

The median LDH levels are plotted in Figure 7.

Figure 7 : Median LDH Levels (C08-003)



The median LDH (U/L) levels were decreased from week 2 up to week 12 and were increased from week 12 to week 26.

Complete TMA Response

Complete TMA Response was defined as hematologic normalization plus improvement in renal function (25% reduction from baseline in serum creatinine maintained for two consecutive measurements for at least 4 weeks). The results of complete TMA response from baseline through 26 weeks as well as the data cutoff date are summarized in Table 24.

Table 24: Complete TMA Response from Baseline through Week 26 and Data Cutoff Date: Study C08-003

	No complement mutation (N=6)	Any complement Mutation (N=14)	Total N=20
Complete TMA response			
No. of patients	2 (33.3%)	3 (21.4%)	5 (25%)
Duration of TMA response from baseline to week 26 (Days)			
Mean (SD)	83 (1.4)	79 (56.3)	81 (39.9)
Median (Min, Max)	83 (82, 84)	111 (14, 112)	84 (82, 112)
Duration of TMA response from baseline to data cutoff date (Days)			
Mean (SD)	175 (129.4)	201 (53)	190 (76.1)
Median (Min, Max)	175 (83, 266)	224 (140, 238)	224 (83, 266)

The complete TMA response was observed in 5 out of 20 patients (25%; 95% CI: (9, 49)) from baseline through week 26 and the data cutoff date. The complete TMA response rates were similar in patients with or without identified complement regulatory factor mutations or auto-antibodies. The median durations of complete TMA response were 84 days and 224 days from

baseline through week 26 and the data cutoff date, respectively. All 5 patients who had achieved a complete TMA response maintained response as of the data cutoff date.

Change in Hemoglobin

The patients whose hemoglobin improved at least ≥ 20 g/L from baseline through week 26 as well as the data cut-off date are summarized in Table 25.

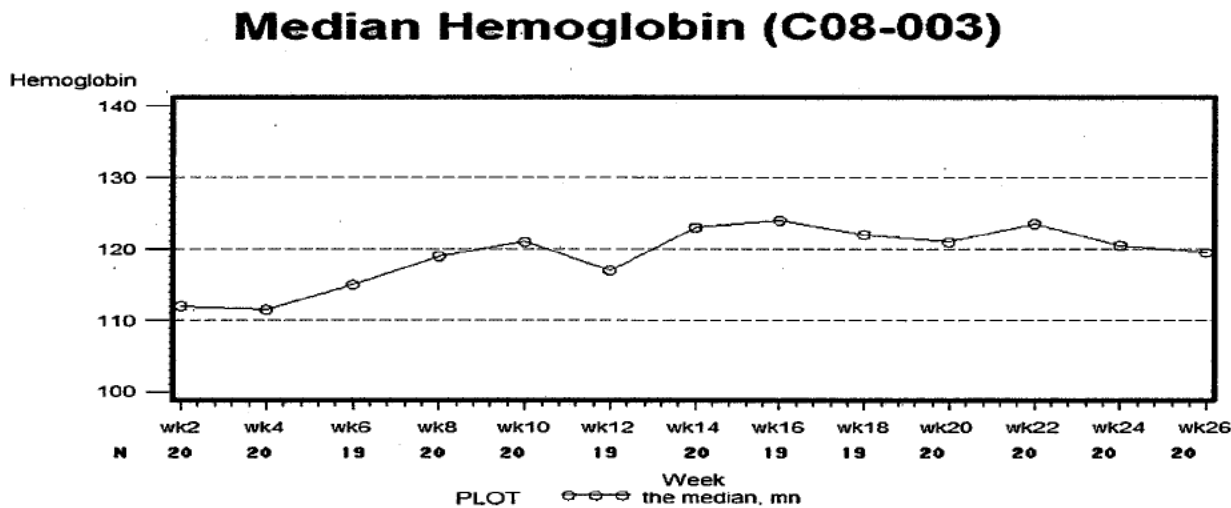
Table 25: Change from Baseline Hemoglobin through Week 26 and Data Cutoff Date: Study C08-003

	No complement mutation (N=6)	Any complement Mutation (N=14)	Total N=20
≥ 20 g/L for at least 2 wks for ≥ 4 wks until week 26			
No. of Patients	3 (50%)	6 (42.9%)	9 (45%)
≥ 20 g/L for at least 2 wks for ≥ 4 wks until data cutoff date			
No. of Patients	3 (50%)	7 (50%)	10 (50%)

Nine out of 20 patients (45%, 95% CI: (23, 68)) had at least two consecutive measurements improvement in at least ≥ 20 g/L for at least 4 weeks from baseline to week 26 and 10 out of 20 (50%, 95% CI: (27, 73)) patients had at least two consecutive measurements improvement in at least ≥ 20 g/L for at least 4 weeks from baseline to the data cutoff date.

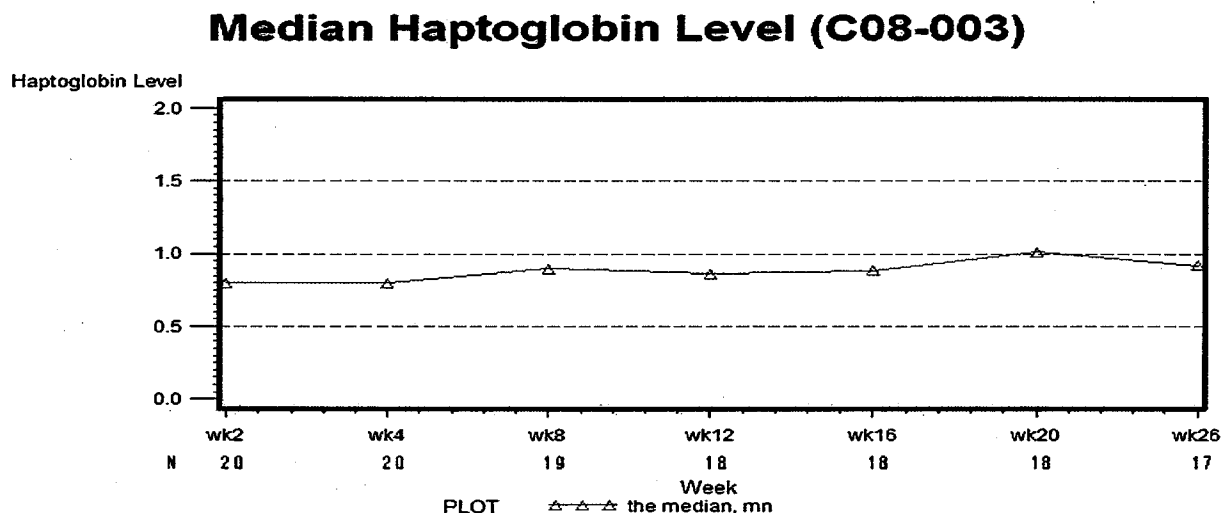
The median hemoglobin levels are plotted in Figure 8.

Figure 8 : Median Hemoglobin Levels (C08-003)



The mean haptoglobin levels were plotted in Figure 9.

Figure 9 : Median Haptoglobin Levels (C08-003)



Median haptoglobin levels were stable between 0.6 g/L to 1 g/L from week 1 through week 26.

Change in Renal Function

The results of change in renal function from baseline through week 26 as well as the data cutoff date are summarized in Table 26.

Table 26: Changes in Renal Function Parameters from Baseline through Week 26 and Data Cutoff Date: Study C08-003

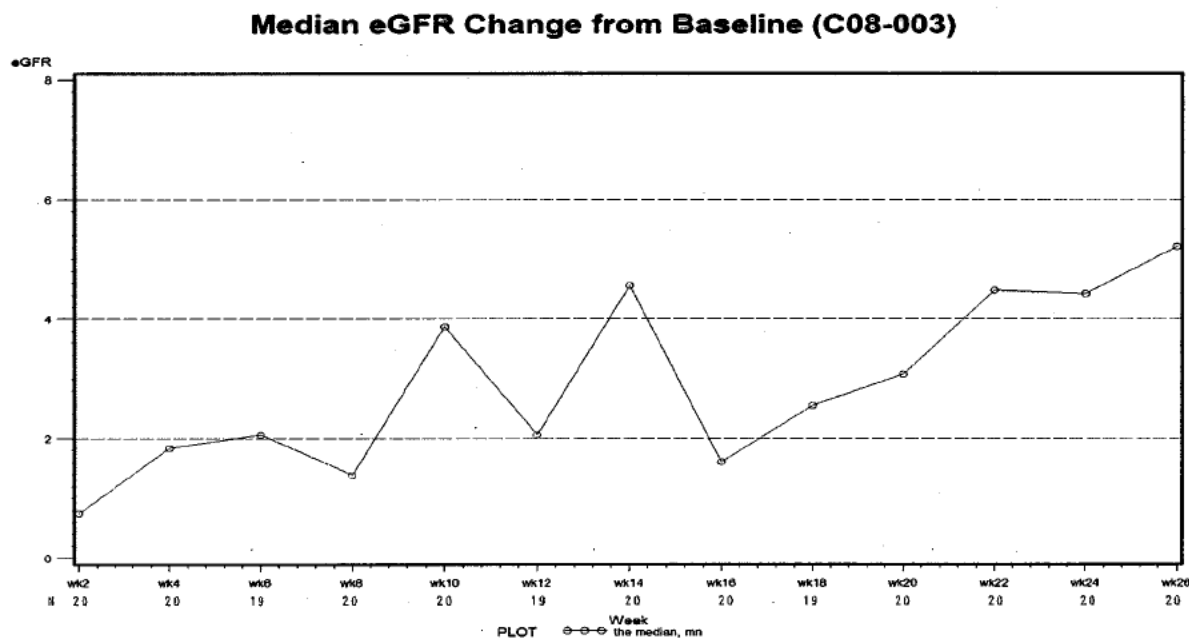
	No complement Mutation (N=6)	Positive for complement mutation (N=14)	Total N=20
eGFR improvement at least 4 weeks from baseline to week 26			
≥ 15 mL/min/1.73m ²	1/6 (16.7%)	0/14	1/20 (5%)
eGFR improvement at least 4 weeks from baseline to data cutoff date			
≥ 15 mL/min/1.73m ²	1/6 (16.7%)	1/14 (7.1%)	2/20 (10%)
CKD Stage improvement at least 4 weeks from baseline to week 26 and data cutoff date			
$\geq$ one stage	3/6 (50%)	4/14 (28.6%)	7/20 (35%)
Creatinine decrease at least 4 weeks from baseline to week 26			
$\leq 25\%$ decrease from Baseline	1/6 (16.7%)	2/14 (14.3%)	3/20 (15%)
Creatinine decrease at least 4 weeks from baseline to data cutoff date			
$\leq 25\%$ decrease from Baseline	1/6 (16.7%)	3/14 (21.4%)	4/20 (20%)

One (5%; 95% CI: (0, 25%)) and two patients (10%; 95% CI: (1, 32)) out of 20 patients maintained at least two scheduled measurements of eGFR ≥ 15 mL/min/1.73 m² for at least 4 weeks until week 26 and until the data cutoff date from baseline levels, respectively. Seven of 20 patients (35%; 95% CI: (15, 59)) maintained improvement in at least one CKD stage from baseline stage for at least 4 weeks through week 26 as well as the data cutoff date from baseline

stage. Three and four out of 20 patients maintained creatinine decrease $\geq 25\%$ from baseline for at least 4 weeks through week 26 and through the data cutoff date, respectively. There was no difference in achieving maintained improvements of renal function parameters between patients with or without identified complement regulatory factor mutation or auto-antibody.

The median eGFR levels change from baseline are plotted in Figure 10.

Figure 10: Median eGFR Change from Baseline (C08-003)



The median of eGFR change from baseline was below 2 mL/min/1.73 m² until week 6 and it was increased from week 20 to week 26.

Efficacy Conclusion for Study C08-003:

- Sixteen out of 20 patients (80%; 95% CI: (56, 94)) achieved the primary endpoint of a TMA event-free status through week 26 as well as the data cutoff date. The median duration of the start day of the TMS event-free status was 84 days. The median duration of TMA event-free status through week 26 and the cutoff date were 181 and 280 days, respectively.
- Eighteen out of 20 patients (90%; 95% CI: (68, 99)) achieved a hematologic normalization from baseline through week 26 as well as the data cutoff date and maintained the normal platelet count after discontinuation of PT and start of eculizumab therapy.
- In the before treatment period (8 weeks prior), only 2 patients had dialysis, no patient was required a TMA intervention (new dialysis and/or PT) after the start of treatment with eculizumab. The median TMA intervention rate was decreased from before treatment of 0.23 events/patient/day to during treatment of 0 events/patient/day through week 26 and

the data cutoff date. The median person days in period 26 weeks and in period data cutoff date were 182 and 282 days, respectively.

- The change from baseline platelet count at each post-dose day of measurement was significantly increased in platelet count from week 2 and week 3. The least square mean change from baseline through week 26 was $5.3 \times 10^9/L$ (95% CI: -17.5, 28.0). There was no difference in platelet count change from baseline from week 4 through week 26 including week 1.
- A total of 18 patients (90%) achieved the platelet count normalization, one out of three patients who had abnormal platelet count at baseline and all 17 patients who had normal platelet count at baseline through week 26 as well as the data cutoff date.
- A total of 19 out of 20 patients (95%; 95% CI: (76, 100)) maintained the decrease in LDH levels below URN from baseline through week 26 as well as the data cutoff date.
- The complete TMA response was observed in 5 out of 20 patients (25%; 95% CI: (9, 49)) from baseline through week 26 and the data cutoff date. The median durations of the complete TMA response were 84 days and 224 days from baseline through week 26 and the data cutoff date, respectively.
- Nine out of 20 patients (45%, 95% CI: (23, 68)) and 10 out of 20 patients (50%, 95% CI: (27, 73)) had at least two consecutive measurements improvement in hemoglobin at least $\geq 20g/L$ for at least 4 weeks from baseline to week 26 and to the data cutoff date, respectively.
- One (5%; 95% CI: (0, 25%)) and two patients (10%; 95% CI: (1, 32)) out of 20 patients maintained at least two scheduled measurements of $eGFR \geq 15 \text{ mL/min/1.73 m}^2$ for at least 4 weeks until week 26 and until the data cutoff date from baseline levels, respectively. Seven of 20 patients (35%; 95% CI: (15, 59) maintained improvement in at least one CKD stage from baseline stage for at least 4 weeks through week 26 as well as the data cutoff date. Three and four out of 20 patients maintained creatinine decrease $\geq 25\%$ from baseline for at least 4 weeks through week 26 and through the data cutoff date, respectively.

3.2.3 Study C09-001r

3.2.3.1 Study Design and Endpoints

Study C09-00r is a retrospective, observational, non-interventional trial to assess eculizumab treatment effect in atypical Hemolytic Uremic Syndrome (aHUS) patients who had received at least one dose of eculizumab between 2007 and Dec 2009, outside of an Alexion-sponsored controlled clinical trial.

Alexion contacted the physicians of the pre-identified patients who had never participated in, nor were concurrently participating in a controlled trial of eculizumab to participate in the retrospective trial. For any patient/treating physician who did not participate in this trial, the reason for not participating was documented as part of the trial documentation. The retrospective data related to a patient's aHUS from the date of aHUS diagnosis up to the date the patient signed the informed consent form (ICF) were collected by their chart review of patient's aHUS

history and eculizumab treatment. The data collection was categorized in four groups: the Initial Pre-Treatment Period; the 30-Day Pre-Treatment Period; the Treatment Period; and the Post Treatment Period.

The efficacy endpoints were normalization of platelet count, TMA intervention rate, TMA event-Free status, normalization of LDH.

The sample size determination was not applicable because this is a retrospective study.

3.2.3.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 36 patients who were diagnosed with aHUS and had been treated with eculizumab were identified. Data from 30 of 36 patients were used for this retrospective trial for analysis. Among 6 patients who were not included in the trial, two patients declined participation and the treating physicians and four other patients declined participation in this retrospective trial.

A total of 11 patients (36.7%) discontinued eculizumab treatment; six patients due to lack of efficacy; two patients due to death, one patient due to an administrative decision; two patients due to renal function normalization.

Demographic characteristics are summarized in Table 27.

Table 27: Patient Demographic Characteristics: Study C09-001r

	All Patients N=30
Age at 1 st dose	
Median (Min, Max)	12 (0.17, 51.4)
< 2 years	5 (16.7%)
≥ 2-<12 years	10 (33.3%)
≥ 12-<18 years	4 (13.3%)
≥ 18 years	11 (36.7%)
Gender	
Female	16 (53.3%)
Male	14 (46.7%)
No. of Patients with Any Complement Regulatory Factor Mutation Or Auto-Antibody Identified	14 (46.7%)
One mutation	13 (43.3%)
Multiple Mutation	1 (3.3%)
Type of Mutation	
Complete Protein 3 (C3) Gain of Function	3 (10%)
Membrane Cofactor Protein (MCP)	1 (3.3%)
Factor H	9 (30%)
Factor H, Factor I, MCP, Factor B Gain of Function	1 (3.3%)

The median age was 12 years with a range of two months to 51 years. The majority of patients were younger than 18 years (19 patients, 63.3%) and 11 patients (36.7%) were older than 18 years. Fourteen patients (46.7%) had complement regulatory factor mutations or auto-antibodies identified, 13 of which had one complement regulatory factor mutation and only one patient had multiple mutations. The remaining 16 patients (53.3%) were not identified any complement regulatory factor mutation or auto-antibodies.

Patients' aHUS and aHUS exacerbation history are summarized in Table 28.

Table 28: Patients' aHUS Exacerbation History: Study C09-001r

	All Population (N=30)
No. of aHUS exacerbation/patient including the 1st diagnosis	
Mean (SD)	3.5 (3.3)
Median (Min, Max)	2 (1, 14)
Time from aHUS diagnosis to 1st dose (Months)	
Mean (SD)	42.3 (56.0)
Median (Min, Max)	10.9 (0.23, 175.9)
Time from current exacerbation to 1st dose (Months)	
Mean (SD)	2.3 (3.0)
Median (Min, Max)	1.2 (0.07, 15.8)
No. of patients with prior kidney transplant	11 (36.7%)
First presentation of aHUS	12 (40%)
No. of patients with current duration of aHUS exacerbation $\leq$ 2 months (PT-resistant-like)	20 (66.7%)
No. of patients with current duration of aHUS exacerbation $>$ 2 months (PT-sensitive-like)	8 (26.7%)
No. of patients without clinical magnification of aHUS	2 (6.7%)

The median of aHUS diagnosed prior to the first dose was of 10.9 months. Fourteen of 30 patients (46.7%) had at least two aHUS exacerbations since initial diagnosis including kidney transplant in 11 patients (36.7%). Twelve patients (40%) were experiencing their first aHUS presentation. The median of experiencing the current aHUS exacerbation prior to the first dose was 1.28 months. Twenty eight of 30 patients had a disease history consistent with PT-resistant and chronic PT populations. The remaining two patients exhibited no clinical manifestations of aHUS; one patient was treated with eculizumab following kidney transplant and the other patient was being prepared for kidney transplant but died of complications of vascular surgery of the carotid artery.

Twenty patients enrolled in this study with aHUS were assessed by the sponsor to be PT-resistant (similar to the prospective Study C08-002A/B) based on a current duration of aHUS exacerbation of $\leq$ 2 months. Eight patients enrolled in this study with aHUS were assessed by the sponsor to be chronic PT (PT-sensitive) patients (similar to the prospective Study C08-003A/B) based on a current duration of aHUS exacerbation of $>$ 2 months.

Current aHUS exacerbation/presentation history is summarized in Table 29.

Table 29: Current aHUS Exacerbation/Presentation History: Study C09-001r

	All Patients (N=30)
Prior to the 1st Dose of Eculizumab	
No. of patients with at least one dialysis	11 (36.7%)
No. of patients with at least one PT	24 (80%)
No. of PT session/patient	
Mean (SD)	8 (6.90)
Median (Min, Max)	8 (0, 29)

Eleven patients (36.7%) required dialysis for renal failure prior to receiving eculizumab. Twenty four patients (80%) received at least one PT session within 28 days prior to the first dose of eculizumab. The median of eight PT sessions was recorded per patient prior to receiving eculizumab.

Baseline laboratory values are summarized in Table 30.

Table 30: Baseline Laboratory Values: Study C09-001r

	All Patients (N=30)
Platelet Count ($\times 10^9/L$)	
Mean (SD)	171.2 (82.9)
Median (Min, Max)	159 (25, 381)
< 150 $\times 10^9/L$	13 (43.3%)
$\geq$ 150 $\times 10^9/L$	17 (56.7%)
LDH (U/L)	N=28
Mean (SD)	602.4 (448)
Median (Min, Max)	453 (158, 1859)
$\leq$ ULN	8 (26.7%)
> ULN	20 (66.7%)
Creatinine ($\mu\text{mol/L}$)	
Mean (SD)	271.1 (277.7)
Median (Min, Max)	159 (15, 968)
eGFR ($\text{mL}/\text{min}/1.73 \cdot \text{m}^2$)	
<15	8 (26.7%)
15-30	5 (16.7%)
30-45	8 (26.7%)
45-60	3 (10%)
60-90	2 (6.7%)
$\geq$ 90	4 (13.3%)
CKD Stage	
Stage 1	4 (13.3%)

Stage 2	2 (6.7%)
Stage 3a	3 (10%)
Stage 3b	8 (26.7%)
Stage 4	5 (16.7%)
Stage 5	8 (26.7%)

Thirteen of 30 patients (43.3%) had low platelet count of $150 \times 10^9/L$ at baseline, and 20 of 30 patients (66.7%) had an LDH level above the ULN at baseline. A total of 24 patients (80%) had an eGFR less than $60 \text{ mL/min/1.73} \times \text{m}^2$. The eGFR was consistent with Stage 4 or Stage 5 chronic kidney disease (CKD) in 13 patients.

3.2.3.3 Statistical Methodologies

The efficacy endpoints were selected based on the two prospective studies. Please refer 3.2.1.3 and 3.2.2.3 statistical methodologies sections.

3.2.3.4 Results and Conclusions

Primary Endpoint

The efficacy endpoint analysis was post-hoc analyses based on the two studies C08-002A/B and C08-003A/B.

Platelet Count Change from Baseline up to Week 52.

Change from baseline platelet count was analyzed at each on-treatment target day until Day 364 using a repeated measurement ANOVA. The results for the estimated least square mean change from baseline platelet count are summarized in Table 31.

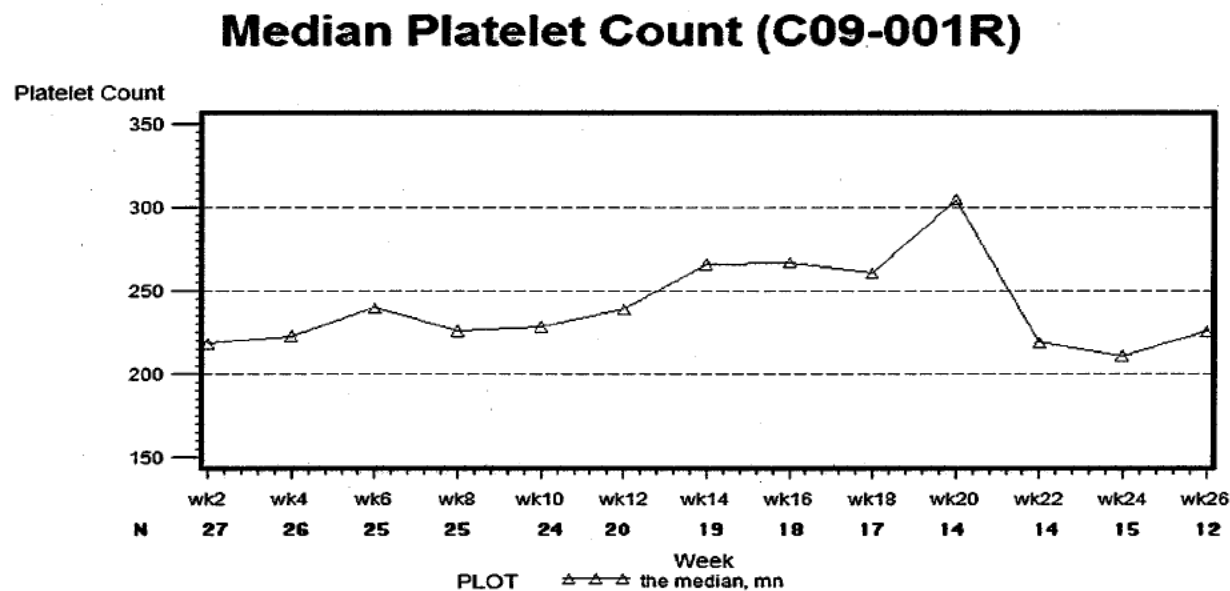
Table 31: Change from Baseline in Platelet Count: Study C09-001r

Time	N	Least square mean	95% CI
Week 2	27	63	(29, 97)
Week 3	23	82	(41, 124)
Week 4	26	71	(36, 107)
Week 26	11	72	(37, 120)
Week 52	5	84	(33, 135)

The mean change from baseline platelet count demonstrated significant increase in platelet count as early as Week 2. However, there were 19 missing (63.3%) in the week 26 and 25 missing (83.3%) at week 52.

The median change in platelet counts are plotted from week 2 through week 26 in Figure 11.

Figure 11: Median Platelet Counts (C09-001r)



The median platelet counts were over 200 x10⁹/L from week 2 through week 26.

Platelet Count Normalization

Platelet count normalization results are summarized in Table 32.

Table 32: Platelet Count Normalization from Baseline through Week 26 and the End of Study: Study C09-001r

Baseline	<150 x10 ⁹ /L (N=13)	≥ 150 x10 ⁹ /L (N=17)	Total (N=30)
Normalization			
Week 26	10/13 (76.9%)	14/17 (82.4%)	24/30 (80%)
End of Study	10/13 (76.9%)	15/17 (88.2%)	25/30 (83.3%)

At baseline, 17 patients had normal platelet count of ≥ 150 x10⁹/L and 13 patients had abnormal platelet count. A total of 24 patients (80%) achieved the platelet count normalization at week 26, 10 out of 13 patients who had abnormal platelet count at baseline and 14 of 17 patients who had normal platelet count at baseline. A total of 25 patients achieved the platelet count normalization at the end of the study.

TMA Intervention Rates

TMA intervention rate results are summarized in Table 33.

Table 33: Summary of TMA Intervention Rate through the Data Cutoff Date: Study C09-001r

	Before treatment	During treatment
TMA Intervention Rate/Patient		
Mean (SD)	0.55 (0.53)	0.03 (0.10)
Median (Min, Max)	0.34 (0, 2.38)	0 (0, 0.41)
No. of patients with pre/new dialysis	11 (36.7%)	2 (0.7%)
No. of pre/new dialysis/patient		
Mean (SD)	4.6 (7.8)	3.2 (13.1)
Median (Min, Max)	0 (0, 29)	0 (0, 66)
No. of patients with any plasma therapies	24 (80%)	9 (30%)
No. of any plasma therapies/patient		
Mean (SD)	8 (6.9)	2.3 (4.3)
Median (Min, Max)	8 (0, 29)	0 (0, 16)
Person days in Period		
Mean (SD)	26.1 (6.7)	278.5 (150.2)
Median (Min, Max)	29 (8, 29)	218 (32, 660)

In the before treatment period (8 weeks prior), 24 patients (80%) had PT and 11 patients (36.7%) had dialysis. There were only two patients who required a TMA intervention (new dialysis and/or PT) after the start of treatment with eculizumab. The median TMA intervention rate was decreased from 0.55 events/patient/day to 0.03 events/patient/day.

TMA Event-Free Status

TMA Event-Free status was defined as the absence for at least 12 weeks of [1] decrease in platelet count of >25% from the baseline Platelet Count; [2] PT while the patient is receiving eculizumab, and [3] new dialysis from baseline through 26 weeks. TMA event-free status is summarized in Table 34.

Table 34: Summary of TMA Event-Free Status through 26 Weeks and the End of study: Study C09-001r

	No complement Mutation (N=16)	Positive for complement mutation (N=14)	Total N=30
No. of TMA Free Status			
At week 26	7/16 (43.8%)	10/14 (71.4%)	17/30 (56.7%)
First Study Day of TMA Free (Days)			
Mean (SD)	95.4 (25.5)	98.8 (28.6)	97.4 (26.6)
Median (Min, Max)	84 (84, 153)	90 (84, 179)	89 (84, 179)
Length of TMA Free (Days)			
At week 26			
Mean (SD)	155.1 (30.4)	152.1 (31.1)	153.4 (29.9)
Median (Min, Max)	174 (111, 181)	164 (84, 180)	164 (84, 181)

A total of 17 among 30 patients (56.7%; 95% CI (37, 75)) achieved TMA event-free status at Week 26. The patients with identified complement regulatory factor mutations or auto-antibodies achieved higher TMA event-free status (71.4%) than patients without mutations in complement regulatory factor (43.8%) at week 26. The median of a conformed TMA event-free status was 89 days and the median duration of maximum TMA status was 164 days with a range of 84 to 181 days. There was no difference in the maximum mean duration days of TMA event-free status between patients with or without identified complement regulatory factor mutations or auto-antibodies.

At the end of the study, three more patients achieved TMA event-free status including two patients without complement regulatory factor mutations or auto-antibodies and one patient with mutation. A total of 20 patients (66.7%; 95% CI (47, 83)) achieved TMA event-free status at the end of the study. The median duration of maximum length of TMA event-free status was 214 days with range of 123 to 646 days.

Change in Hemoglobin

The patients whose hemoglobin improved at least 20 g/L for at least 4 weeks from baseline through week 26 as well as through the data cutoff date are summarized in Table 35.

Table 35: Change from Baseline Hemoglobin through Week 26: Study C09-001r

	No complement mutation (N=16)	Any complement Mutation (N=14)	Total N=30
≥20 g/L for at least 2 wks for ≥4 wks			
No. of Patients	5 (31.3%)	7 (50%)	12 (40%)

A total of 12 patients (40%; 95% CI: (23, 59)) maintained the improvement in hemoglobin at least 20 g/L for at least 4 weeks from baseline to week 26. There was no difference in maintained hemoglobin improvement between patients' with or without identified complement regulatory factor mutations or auto-antibodies.

The change from baseline hemoglobin levels are summarized in Table 36.

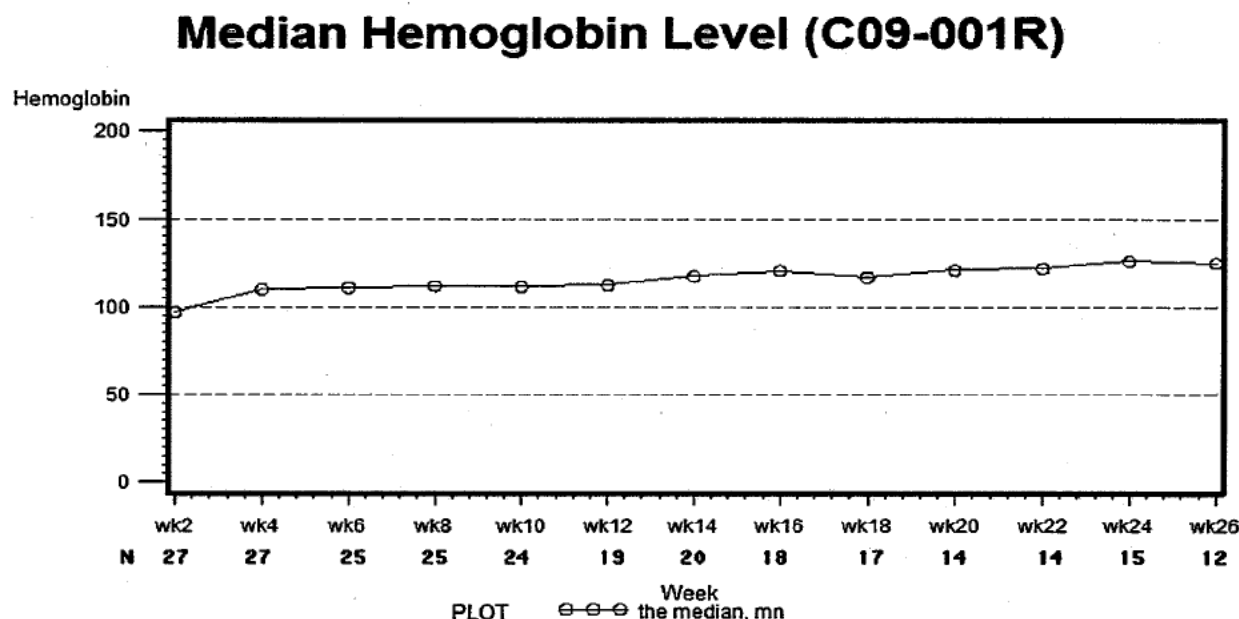
Table 36: Change from Baseline Hemoglobin: Study C09-001r

Time	N	Mean (SD)	Median (Min, Max)
Week 1	30	3.8 (15.0)	0 (-24, 46)
Week 2	27	3.0 (18.5)	-2.0 (-33, 42)
Week 3	23	3.4 (16.1)	5.0 (-38, 28)
Week 4	26	9.8 (26.8)	6.0 (33, 101)
Week 26	11	23.9 (18.9)	21.0 (-6, 51)
Week 52	5	17.9 (22.1)	25.0 (-11.3, 39)

At week 26, only 12 patients' hemoglobin levels were available.

The median hemoglobin levels are plotted in Figure 12.

Figure 12: Median Hemoglobin Levels (C09-001r)



The median hemoglobin levels were stable between 100 g/L and 150 g/L from week 2 through week 26.

LDH

The patients' LDH levels below the upper limit (URN) of its normal range from baseline through week 26 are summarized in Table 37.

Table 37: LDH Levels: Study C09-001r

	No complement Mutation (N=16)	Any complement Mutation (N=14)	Total N=30
LDH <URN at least 2 wks for ≥4 wks			
No. of patients	5 (31.3%)	12/14 (70.6%)	17/30 (56.7%)

A total of 17 among 30 patients (56.7%; 95% CI: (37, 75) maintained LDH levels below the ULN at least 2 weeks for at least 4 weeks until week 26. Twelve patients (70.6%) with identified complement regulatory factor mutations maintained LDH below the ULN from baseline through week 26 compared to 5 patients (31.3%) with no identified complement regulatory factor mutations or auto-antibodies.

Reviewer's comment:

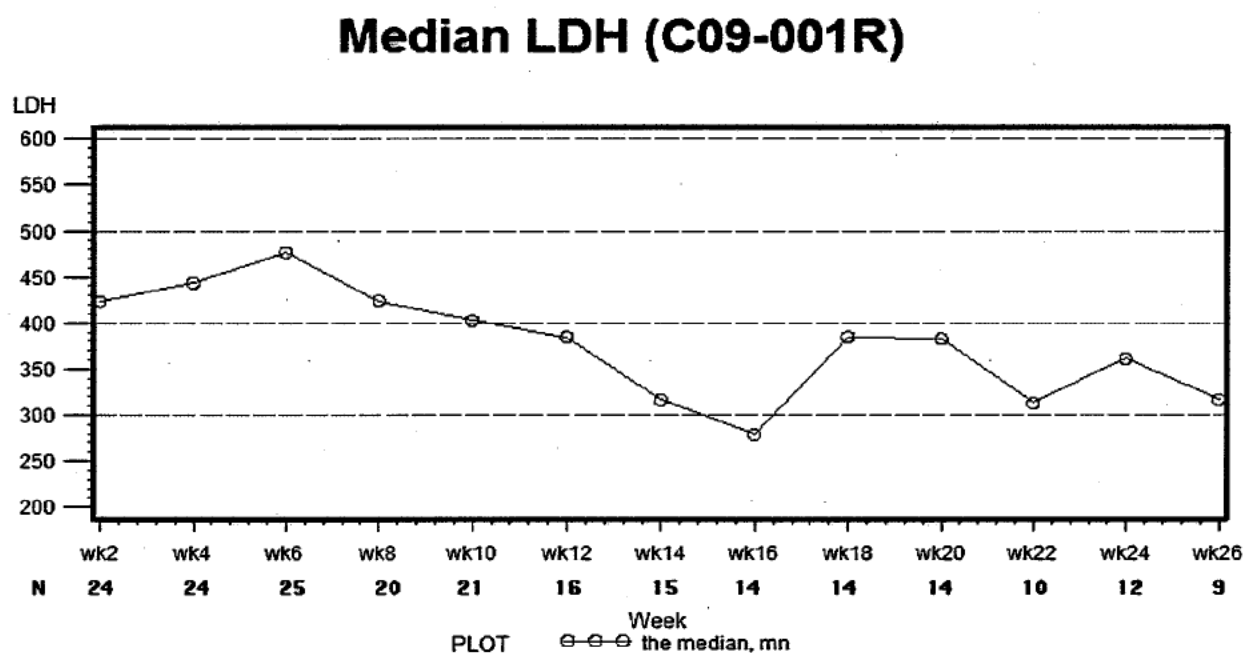
Change from baseline LDH levels are summarized in Table 38.

Table 38: Change from Baseline LDH Levels: Study C09-001r

Time	N	Mean (SD)	Median (Min, Max)
Week 1	25	-155 (247.9)	-28 (-879, 108)
Week 2	24	-159 (365.4)	-59 (-1162, 491)
Week 3	18	-239 (415.0)	-112 (-1268, 120)
Week 4	24	-177 (367.6)	-60 (-1312, 357)
Week 26	8	-398 (616.4)	-71 (-1506, 6)
Week 52	4	-410 (520.2)	-231 (-1190, -9)

The median LDH levels are plotted in Figure 13.

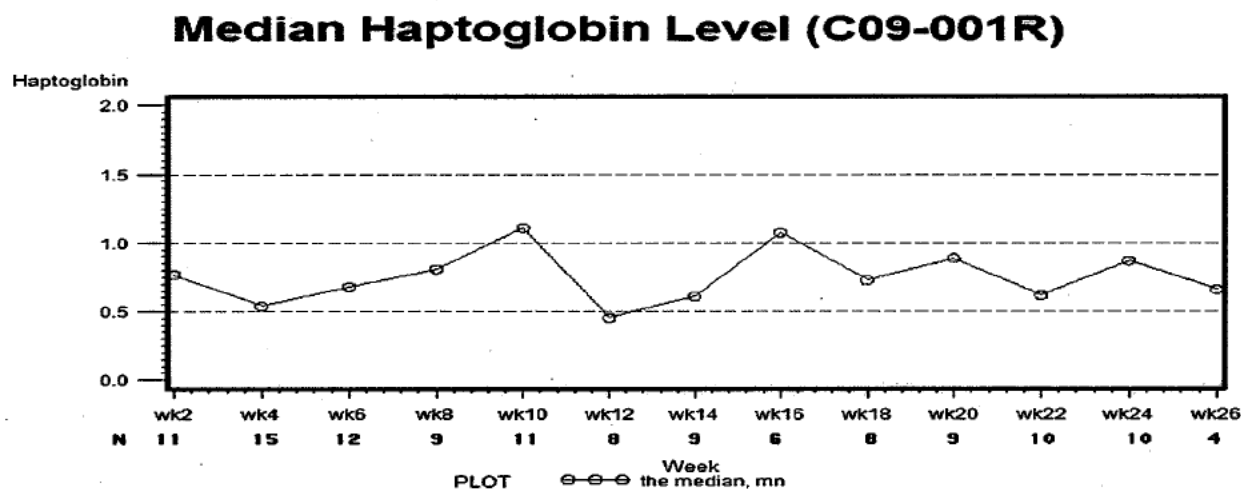
Figure 13: Median LDH Levels (C09-001r)



The median LDH levels were increased above 400 URN from week 2 through week 6, decreased up to 300 URN from week 6 through week 16, increased above 350 URN at week 16 and maintained between 300 and 350 URN through week 26.

The median haptoglobin levels are plotted in Figure 14.

Figure 14: Median Haptoglobin Level (C09-001r)



The median haptoglobin levels were between 0.5 to 1 g/L from week 2 through week 26.

Renal Function Parameters

The renal function parameters are summarized in Table 39.

Table 39: Changes in Renal Function Parameters from Baseline through Week 26 and Data Cutoff Date: Study C09-001r

	No complement Mutation (N=16)	Positive for complement mutation (N=14)	Total N=30
eGFR improvement at least 4 weeks from baseline to week 26 & end of study $\geq 15 \text{ mL/min/1.73m}^2$	6/16 (37.5%)	5/14 (35.7%)	11/30 (36.7%)
CKD Stage improvement at least 4 weeks from baseline to week 26 & end of study $\geq$ one stage	7/16 (50%)	5/14 (35.7%)	12/30 (40%)
Creatinine decrease at least 4 weeks from baseline to week 26 & end of study $\leq 25\%$ decrease from Baseline	7/16 (16.7%)	5/14 (14.3%)	12/30 (40%)

Eleven (36.7%; 95% CI: (20, 56)) out of 30 patients maintained at least two scheduled measurements of eGFR $\geq 15 \text{ mL/min/1.73 m}^2$ for at least 4 weeks until week 26 and until the end of the study from baseline levels. Twelve of 30 patients (40%; 95% CI: (23, 59)) maintained improvement in CKD stage of one stage from baseline for at least 4 weeks through week 26 as well as end of study. Twelve out of 30 patients (40%; 95% CI (23, 59)) maintained creatinine decrease of $\geq 25\%$ from baseline at least 4 weeks through week 26 as well as the end of the study.

Hematologic normalization and complete TMA responses

The composite endpoints of hematologic normalization and complete TMA response, the pre-specified analyses used in the two prospective studies, C08-002 and C08-003, had important analytical limitations in this trial. Due to these limitations, a sponsor assessment was performed using criteria similar to those which were applied in the prospective studies. The categories of responses were used as follows:

Hematologic normalization: Normalization of platelet count and LDH levels in patients who had abnormal platelet counts at baseline or immediately prior to baseline. The LDH criterion was waived if no LDH measurement was reported during eculizumab therapy.

Ten out of 30 patients (33.3%) achieved a hematologic normalization.

Complete TMA response: Hematologic normalization and improvement in renal function, defined as a $\geq 25\%$ decrease in serum creatinine from baseline.

Ten out of 30 patients (33.3%) achieved complete TMA responses.

Efficacy Conclusion for Study C09-001r

- The mean change from baseline platelet count was significantly increased as early as week 2. However, there were 19 missing (63.3%) in the week 26 and 25 missing (83.3%) at week 52.
- In the before treatment period (8 weeks prior), 24 patients (80%) had PT and 11 patients (36.7%) had dialysis. There were only two patients who required a TMA intervention (new dialysis and/or PT) after the start of treatment with eculizumab. The median TMA intervention rate was decreased from before treatment of 0.55 events/patient/day to during treatment of 0.03 events/patient/day.
- A total of 17 among 30 patients (56.7%; 95% CI (37%, 75%)) achieved TMA event-free status at week 26. The patients with identified complement regulatory factor mutations or auto-antibodies achieved higher TMA event-free status (71.4%) than patients without mutations in complement regulatory factor (43.8%) at week 26. The median of a conformed TMA event-free status was 89 days and the median duration of maximum TMA status was 164 days with a range of 84 to 181 days. A total of 20 patients (66.7%; 95% CI (47, 83)) achieved TMA event-free status at the end of the study. The median duration of maximum length of TMA event-free status was 214 days with range of 123 to 646 days.
- A total of 12 patients (40%; 95% CI: (23, 59)) maintained the improvement in hemoglobin at least ≥ 20 g/L for at least 4 weeks from baseline to week 26.
- A total of 17 among 30 patients (56.7%; 95% CI: (37, 75)) maintained LDH levels below the ULN for at least 4 weeks until week 26. Twelve patients (70.6%) with identified complement regulatory factor mutations maintained LDH below the ULN from baseline through week 26 compared to 5 patients (31.3%) with no identified complement regulatory factor mutations or auto-antibodies.
- Eleven patients (36.7%; 95% CI: (20, 56)) out of 30 patients maintained at least two scheduled measurements of eGFR ≥ 15 mL/min/1.73 m² for at least 4 weeks until week

26 and until the end of study from baseline levels. Twelve of 30 patients (40%; 95% CI: (23, 59)) maintained improvement in CKD stage of one stage from baseline for at least 4 weeks through week 26 as well as the end of study. Twelve out of 30 patients (40%; 95% CI (23, 59)) maintained creatinine decrease of $\geq 25\%$ from baseline at least 4 weeks through week 26 as well as the end of study.

- Ten patients (33.3%) achieved hematologic normalizations and complete TMA responses based on the sponsor assessed criteria that were different from that of the two prospective studies.

3.3 Evaluation of Safety

For a detailed summary of the evaluation of safety refer to the review by Dr. Martha Donoghue.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Two prospective studies of C08-002 and C08-003 and one retrospective study of C09-001r are all single arm studies with sample sizes of 17, 20 and 30, respectively. The subgroup analyses are omitted due to lack of representation of limited sample sizes.

There are 15 pediatric patients of age <12 years old in the Study C09-001r. The efficacy analyses for those 15 pediatric patients are summarized in Table 40.

Table 40 : Efficacy Results for Pediatric Patients of Age <12 years old: Study C09-001r

	Age <12 years old (N=15) n/N, (%)
Platelet normalization	14/15 (93.3)
TMA event-free status	11/15 (73.3)
TMA intervention rate –Median (Min, Max)	
Before Treatment	<1 (0, 2.38)
During Treatment	0 (0, <1)
eGFR improvement ≥ 15 mL/min/1.73m ²	8/15 (53.3)
Improved ≥ 1 CKD stage	2/15 (13.3)
Hemoglobin increase >20 g/L	8/15 (53.3)
Sponsor assessed Hematologic normalization and Complete TMA response	7/14 (50)

A total of 14 patients (93.3%) achieved the platelet count normalization. A total of 11 patients (73.3%) achieved TMA event-free status at the end of study. The median TMA intervention rate was decreased from before treatment of <1 events/patient/day to during treatment of 0

events/patient/day. The renal function parameters were also improved. Seven patients (50%) achieved hematologic normalizations and complete TMA responses based on the sponsor assessed criteria which are different from that of the two prospective studies.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The key statistical issues and findings that impact them, with regards to the demonstration of efficacy are summarized as follows:

- These two studies are single arm study with very small sample sizes, 17 for study C08-002 and 20 for study C08-003, so there may be limitations for the risk-benefit determination.
- For the retrospective study, 11 patients (36.7%) discontinued the study drug among the sample size of 30 patients and 19 patients were missing at week 26 and 25 patients were missing at week 52. Because of early dropouts, the long-term efficacy results are not reliable.
- The applicant's inferential tests are not appropriate because of single arm studies with very small sample sizes. P-values should not be included in the labeling.

For prospective studies;

- Study C08-002's primary endpoint of platelet count change from baseline was significantly increased from week 1 through week 26 and 14 out of 17 patients (82.4%) achieved the platelet count normalization. For study C08-003, the normal platelet count was maintained from baseline through week 26 and 18 out of 20 patients achieved the platelet count normalization.
- For study C08-002's the other primary endpoint of hematologic normalization, 13 out of 17 patients (76.5%) achieved a hematologic normalization (95% CI: (50, 93)) through week 26 as well as the data cutoff date. For study C08-003, 18 out of 20 patients (90%: 95% CI: (68, 99)) achieved a hematologic normalization from baseline through week 26 as well as the data cutoff date.
- For study C08-002, the complete TMA response was observed in 11 out of 17 patients (64.7%; 95% CI: (38, 96)) from baseline through week 26 and the data cutoff date. For study C08-003, the complete TMA response was observed in 5 out of 20 patients (25%; 95% CI: (9, 49)) from baseline through week 26 and the data cutoff date.
- For the study C08-003's primary endpoint of TMA event-free status, 16 out of 20 patients (80%: 95% CI (56, 94)) achieved TMA event-free status through week 26 as well as the data cutoff date. Fifteen out of 17 patients (88.2%:95% CI (64, 99)) achieved TMA event-free status from baseline through week 26 and the data cutoff date in the study C08-002.
- Study C08-002's TMA intervention rate was 0.88 for before the treatment period and was decreased to 0 during the treatment period. Study C08-003's TMA intervention rate was decreased from before treatment of 0.23 to during treatment of 0.

- For the study C08-002 renal function changes, 8 (47.1%; 95% CI: (23, 72)) and 9 patients (52.9%; 95% CI: (28, 77)) out of 17 patients maintained at least two scheduled measurements of eGFR $\geq$ 15 mL/min/1.73 m² for at least 4 weeks until week 26 and until the data cutoff date from baseline levels, respectively. Ten of 17 patients (59%; 95% CI: (33, 82)) maintained improvements in at least one CKD stage for at least 4 weeks through week 26 as well as the data cutoff date from baseline stage. Eleven out of 17 (64.7%; 95% CI (38, 86)) patients maintained creatinine decrease of $\geq$ 25% from baseline for at least 4 weeks through week 26 as well as the data cutoff date from baseline levels.
- For the study C08-003 renal function changes, one (5%; 95% CI: (0, 25%)) and two patients (10%; 95% CI: (1, 32)) out of 20 patients maintained at least two scheduled measurements of eGFR $\geq$ 15 mL/min/1.73 m² for at least 4 weeks until week 26 and until the data cutoff date from baseline levels, respectively. Seven of 20 patients (35%; 95% CI: (15, 59)) maintained improvements in at least one CKD stage from baseline stage for at least 4 weeks through week 26 as well as the data cutoff date. Three and four out of 20 patients maintained creatinine decrease of $\geq$ 25% from baseline for at least 4 weeks through week 26 and through the data cutoff date, respectively.

For retrospective study;

- A total of 24 patients (80%) achieved the platelet count normalization at week 26, 10 out of 13 patients who had abnormal platelet count at baseline and 14 of 17 patients who had normal platelet count at baseline.
- In the before treatment period (8 weeks prior), 24 patients (80%) had PT and 11 patients (36.7%) had dialysis. There were only two patients who required a TMA intervention (new dialysis and/or PT) after the start of treatment with eculizumab. The median TMA intervention rate was decreased from before treatment of 0.55 events/patient/day to during treatment of 0.03 events/patient/day.
- A total of 17 (56.7%; 95% CI (37%, 75%)) and 20 (66.7%; 95% CI (47, 83)) among 30 patients achieved TMA event-free status at week 26 and at the end of study, respectively.
- Ten patients (33.3%) achieved hematologic normalizations and complete TMA responses based on the sponsor assessed criteria that are different from that of the two prospective studies.
- The efficacy results for pediatric patients of age <12 years old were similar to that of C09-001r.

5.2 Conclusions and Recommendations

Two prospective studies, Study C08-002 and Study C08-003 observed efficacy results reasonably likely provide sufficient evidence for the clinical benefit in PT-resistant and in PT-sensitive aHUS adult patients. For Study C09-001r, the efficacy results were similar to the two prospective studies through week 26 and through the end of the study. However, after week 26, large percent of patients dropped out of the study.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Kyung Yul Lee, Ph.D.

Kyung Yul Lee

Date: 8/24/2011

Concurring Reviewer(s):

Mark Rothmann 8/24/2011
I concur

Statistical Team Leader: Mark Rothmann, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

RS 8/24/2011

cc:

Project Manager: MS. Ali Ibrahim

Medical Officer: DR. Martha Donoghue

Primary Statistical Reviewer: Kyung Yul Lee, Ph.D.

Statistical Team Leader: Mark Rothmann, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

Lillian Patrician

c:\BLA\statreview.doc

CHECK LIST

Number of Pivotal Studies: 3

Trial Specification

Specify for each trial:

Protocol Number (s): C08-002, C08-003, C09-001r

Protocol Title (optional):

Phase: 2

Control: No Control

Blinding: Open-Label

Number of Centers: 15

Region(s) (Country): C08-002 (10 in Europe and 7 in US/Canada) , C08-003, (18 in Europe and 2 in US/Canada), C09-001r (16 in Europe, 13 in USA and 1 in Canada)

Duration: 26 Weeks

Treatment Arms: Eculizumab

Treatment Schedule: The does of 600mg, 900mg, or 1,200mg was administered intravenously for induction period, week 5 and maintenance period during the first 26 weeks treatment.

Randomization: No

Primary Endpoint: C08-002: Change from baseline platelet count and hematologic normalization if the change from platelet count from baseline is significant.

C08-003: TMA event-free and hematologic normalization if TMA-event free is significant.

C09-001r: Look at all the primary endpoints of C08-002 and C08-003

Primary Analysis Population: ITT (all treated patients)

Statistical Design: single arms

Primary Statistical Methodology: C08-002: Platelet count change from baseline: repeated measure ANOVA Other endpoints: point estimates and exact 95% CIs; Descriptive statistics

C08-003: TMA event-free status: exact 95% CIs; Descriptive statistics

Interim Analysis: No

DSMB: No

Sample Size: C08-002 (N=17), C08-003 (N=20), C09-001r(N=30)

Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable?

C08-002: The sample size was planned at least 12 patients assuming a null hypothesis of no post-dose change from baseline in mean platelet count, the study had approximately 88% power to detect as statistically significant an effect size (mean change from baseline / standard deviation) of at least one when using a one sample t-test with a two-sided $\alpha = 0.05$.

C08-003: The sample size was planned as 20 patients assuming that the true expected probability of TMA event-free exacerbation-treated patient is 40%, the study had approximately 93.5% statistical power to detect a statistically significant difference from a minimum probability

of 10%, 80.8% when a minimum probability of 15%, and 61.0% when a minimum probability of 20%.

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No
- Were the **Covariates** pre-specified in the protocol? No
- Did the Applicant perform **Sensitivity Analyses**? No
- How were the **Missing Data** handled? LOCF
- Was there a **Multiplicity** involved? No
If yes,
Multiple Arms (Yes/No)?
Multiple Endpoints (Yes/No)? Yes
Which method was used to control for type I error?
- **Multiple Secondary Endpoints:** Are they being included in the label? If yes, method to control for type 1 error. Secondary endpoints are described as the proposed label (without control of type 1 error).
Were Subgroup Analyses Performed (Yes/No)? No
- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report?
No
- Overall, was the study positive (Yes/No)? Yes

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 125166

Applicant: Alexion Pharmaceuticals

Stamp Date: 3/25/2011

Drug Name: eculizumab

NDA/BLA Type: BLA

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			No define.pdf files

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

<u>Kyung Yul Lee</u>	<u>4/20/2011</u>
Reviewing Statistician	Date
<u>Mark Rothmann</u>	<u>4/20/2011</u>
Supervisor/Team Leader	Date

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125166s172

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

BLA	125166
Type/Category	New indication, efficacy supplement
Brand Name	SOLIRIS
Generic name	Eculizumab
Proposed Indication	Treatment atypical hemolytic uremic syndrome (aHUS)
Dosage Form	Injection
Route of Administration	Subcutaneous
Dosing Regimen and Strength	Many (See Section 2.1.3)
Applicant	Alexion Pharmaceuticals
OCP Division	Clinical Pharmacology 5
OND Division	Division of Hematology Products
Submission Date	25-March-2011
Primary Reviewer	Bahru A. Habtemariam, PharmD
Secondary Reviewer	Julie Bullock, PharmD
Pharmacometrics Secondary Reviewer	Christine Garnett, PharmD

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1 EXECUTIVE SUMMARY

Eculizumab is a humanized IgG_{2/4} kappa monoclonal antibody that inhibits the cleavage of the complement protein C5 to C5a and C5b, which in turn prevents the generation of the terminal complement complex C5b-9. Eculizumab was approved on March 16, 2007 for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. The approved maintenance doses were: 600 mg weekly for 4 weeks, 900 mg on week 5, and 900 mg every 14 days thereafter.

In the current submission, the applicant proposes a new indication for the treatment of patients with atypical hemolytic uremic syndrome (aHUS). The proposed eculizumab dose for adults and children weighing ≥ 40 kg is 900 mg weekly for 4 weeks, 1200 mg on weeks 5, and 1200 mg every 2 weeks thereafter. For patients less than 18 years old that weight < 40 kg, the sponsor proposed the following weight based induction and maintenance dosing regimens:

- Weight 30- <40 kg: 600 mg weekly x 2; 900 mg on week 3; then 900 mg Q2 wks
- Weight 20- <30 kg: 600 mg weekly x 2; 600 mg on week 3; then 600 mg Q2 wks
- Weight 10- <20 kg: 600 mg weekly x 1; 300 mg on week 2; then 300 mg Q2 wks
- Weight 5- <10 kg: 300 mg weekly x 1; 300 mg on week 2; then 300 mg Q3 wks

To support the current indication, the sponsor conducted two prospective trials in adolescents and adults (studies C08-002 (n=17) and C08-003 (n=20)) and one retrospective trial in children and adults (study C09-001r (n=30)). The primary endpoints for studies C08-002 and C08-003 were change in platelet count and thrombotic microangiopathy (TMA) events-free status, respectively. Additional endpoints used to evaluate the efficacy of eculizumab were change in renal function, change in hemoglobin, quality of life (QoL) measure, hematologic normalization, and complete TMA response. As outlined in the QBRs section below, clinical improvements were reported for all endpoints.

For the proposed doses, predicted steady state AUC (AUC_{ss}) was comparable across all weight categories.

Exposure-response (ER) analyses were performed for three of the eight endpoints including TMA event-free status, change in renal function, and hematologic normalization. The analyses showed that proportion of patients with TMA event-free status, hematologic normalization, and GFR improvement > 15 mL/min was not influenced by eculizumab AUC_{ss}, patient weight or age.

The safety endpoints investigated using exposure-response analyses were infection and hypertension. ER analyses showed that proportion of patients with infection or hypertension did not increase with increasing eculizumab concentrations.

1.1 RECOMMENDATIONS

The overall clinical pharmacology data submitted to support the approval of this supplemental BLA are acceptable provided that a satisfactory agreement is reached regarding the labeling.

There are no clinical pharmacology post-marketing requirements or commitments identified for this sBLA. The sponsor should consider the following comment as their drug development for

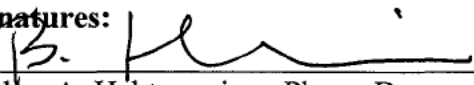
this indication proceeds:

- The sponsor should submit PK and efficacy data from the ongoing pediatric clinical trial. The sponsor should update population PK model using data from the ongoing pediatric trial.

1.2 LABELING RECOMMENDATIONS

Please refer to Section 3 - Detailed Labeling Recommendations

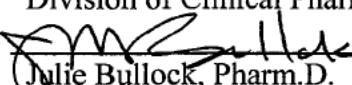
Signatures:

 9.01.11

Bahru A. Habtemariam, Pharm.D.

Reviewer

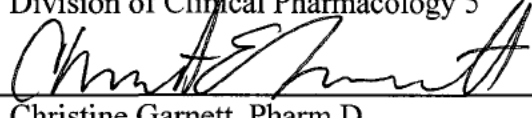
Division of Clinical Pharmacology 5

 9.1.11

Julie Bullock, Pharm.D.

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 9/01/2011

Christine Garnett, Pharm.D.

Pharmacometrics Team Leader

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CC DCP-5: DDD – B Booth; DD – NA Rahman

DPM: DD – J Gobburu

1.3 CLINICAL PHARMACOLOGY SUMMARY

Eculizumab (Soliris[®]) is a monoclonal antibody that binds to the complement protein C5, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Eculizumab inhibits terminal complement mediated intravascular hemolysis in PNH and aHUS patients.

The original BLA for eculizumab was approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) on March 16, 2007. The dosing regimen for the PNH indication consisted of an induction dose (600 mg weekly for four weeks) and a maintenance dose (900 mg on week 5 plus 900 mg every two weeks thereafter).

In the present submission, the sponsor is seeking a new indication for the treatment of patients with aHUS. Similar to the PNH indication, the proposed dosing regimen for the aHUS indication also consists of induction and maintenance doses. For adults and children that weigh ≥ 40 kg, the proposed induction dose is 900 mg weekly for 4 weeks, while the proposed maintenance doses are 1200 mg on week 5 followed by 1200 mg every 2 weeks thereafter. The proposed doses for children (age < 18 years old) that weigh < 40 mg are based on weight breakdowns as shown in **Table 1**.

To support the proposed aHUS indication, the sponsor conducted two prospective trials (studies C08-002 and C08-003) in adults and adolescents and one retrospective trial (study C09-001r) in adults and children. The primary endpoint for study C08-002 was change in platelet count at week 26. The primary endpoint for study C08-003 was number of patients with TMA event free status at week 26. Study C09-001r did not have a primary endpoint. A total of eight endpoints were used to assess efficacy eculizumab in each study (**Table 4**).

Population pharmacokinetics analysis showed body weight as a covariate for clearance and volume, which supports the use of weight cut-offs for dosing in children. The typical clearance, volume, and half-life parameters of eculizumab, for a 70 kg adult patient, were estimated to be 0.0146 L/hr, 6.14 L, and 12.4 days, respectively. The clearance of eculizumab for each weight category is summarized in **Table 7**. In patients with plasma intervention, the clearance of eculizumab was increased to 3.66 L/hr, reducing the half-life of eculizumab to 4.26 hours.

An ER relationship was evaluated for three clinical endpoints: TMA event-free status, change in renal function, and hematologic normalization. Model-predicted AUC_{ss} for the maintenance dosing regimen was used as the exposure variable. An ER relationship could not be identified for these three endpoints. Furthermore, there were no significant trends for these endpoints with patient weight or age.

Infection and hypertension were identified as important safety endpoints for eculizumab. Infection is thought to arise from the mechanism of action of the drug while hypertension maybe due to the natural history of the disease. No ER relationship could be identified for these safety endpoints.

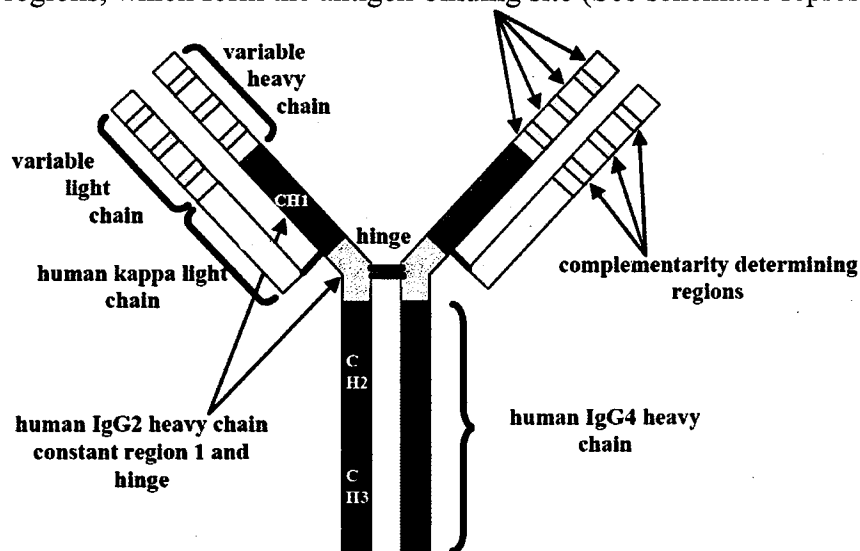
2 QUESTION BASED REVIEW

Eculizumab has been reviewed previously under BLA 125166 for adult paroxysmal nocturnal hemoglobinuria (PNH) indication. The original BLA was submitted on September 15, 2006 and subsequently approved on March 16, 2007. For brevity, only QBR questions regarding the current sBLA submission will be addressed below.

2.1 GENERAL ATTRIBUTES OF THE THERAPEUTIC PROTEIN

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The eculizumab antibody (h5G1.1-mAb) is a humanized IgG_{2/4} kappa antibody, consisting of two 448 amino acid heavy chains and two 214 amino acid light chains. The heavy chains are comprised of human IgG2 sequences in constant region 1, the hinge, and the adjacent portion of constant region 2, and human IgG4 sequences in the remaining part of constant region 2 and constant region 3. The light chains are comprised of human kappa sequences. The variable chains consist of human framework regions with grafted murine complementarity-determining regions, which form the antigen-binding site (See schematic representation below).



- Established name: Eculizumab
- Molecular Weight: 148 kda

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Eculizumab is a monoclonal antibody that 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. Eculizumab inhibits terminal complement mediated intravascular hemolysis in complement-mediated thrombotic microangiopathy (TMA) in aHUS patients. aHUS patients have chronic systemic uncontrolled complement activation associated with clotting in small vessels across the body. Clinically, complement-mediated TMA causes seizures, strokes, myocardial infarction, pulmonary insufficiency, and renal insufficiency and/or failure with frequent fatal outcomes.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose of eculizumab for adults and pediatric patients is shown in **Table 1**. While adults and children weighing ≥ 40 kg are given flat doses, the doses for children weighing < 40 kg are determined based on weight cut-offs.

Table 1. Proposed adult and pediatric eculizumab doses.

	Induction	Maintenance
Adult & pediatric patients ≥ 40 kg	900 mg weekly x 4	1200 mg on week 5; then 1200 mg Q2 wks
Pediatric patients < 40 kg		
30- <40 kg	600 mg weekly x 2	900 mg on week 3; then 900 mg Q2 wks
20- <30 kg	600 mg weekly x 2	600 mg on week 3; then 600 mg Q2 wks
10- <20 kg	600 mg weekly x 1	300 mg on week 2; then 300 mg Q2 wks
5- <10 kg	300 mg weekly x 1	300 mg on week 2; then 300 mg Q3 wks

2.2 GENERAL CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor conducted three clinical studies (**Table 2**). Two of the three clinical studies were prospective single arm studies where patients were treated with induction dose of 900 mg weekly for 4 weeks, followed by maintenance dose of 1200 mg every 2 weeks. The third study, study C09-001r, was a retrospective study in children and adults (age range 0.2 – 67 years), where adults patients were treated using similar induction and maintenance doses, whereas children that weigh < 40 kg were treated using lower induction/ maintenance doses (see **Table 1**). For the prospective study, efficacy, safety, and PK data were collected retrospectively from the patients chart. Pharmacokinetics data were available from all patients that took part in the prospective studies and 20 of the 30 patients that took part in the retrospective trials (**Table 2**).

Table 2. Summaries of clinical studies submitted to support adult and pediatric aHUS indications

Study	N	Patient Characteristics	PK Subset	Clinical endpoints
C08-002	17	Adult (Age > 17 years old)	All	See section 2.3
C08-003	20	Adult and Adolescents (Age > 14 years)	All	See section 2.3
C09-001r	30	Adult and Children (Age > 0.2 years)	20	See section 2.3

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Eculizumab the circulating moiety and it was measured using a validated, conventional sandwich enzyme-linked immunosorbent assay (ELISA). See the original BLA review for analytical method.

2.3 EXPOSURE-RESPONSE

2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Eculizumab works by binding to free C5 and preventing the conversion of C5 to C5a and C5b. Therefore, decreasing the amount of free C5 in the circulation is thought to decrease the clinical manifestations of aHUS. **Figure 1** shows the concentration-effect relationship for free C5. The minimum eculizumab concentration required to decrease free C5 by > 90% is estimated to be 50 µg/mL. The doses of eculizumab for the submitted clinical studies were targeted to achieve minimal eculizumab concentrations of 50 µg/mL. Simulated eculizumab trough concentrations following first induction dose and steady-state maintenance dose show concentrations mostly stay at > 50 µg/mL (**Table 3**). Cmin and Cmax values were simulated using appropriate doses for each weight category as shown in **Table 1**.

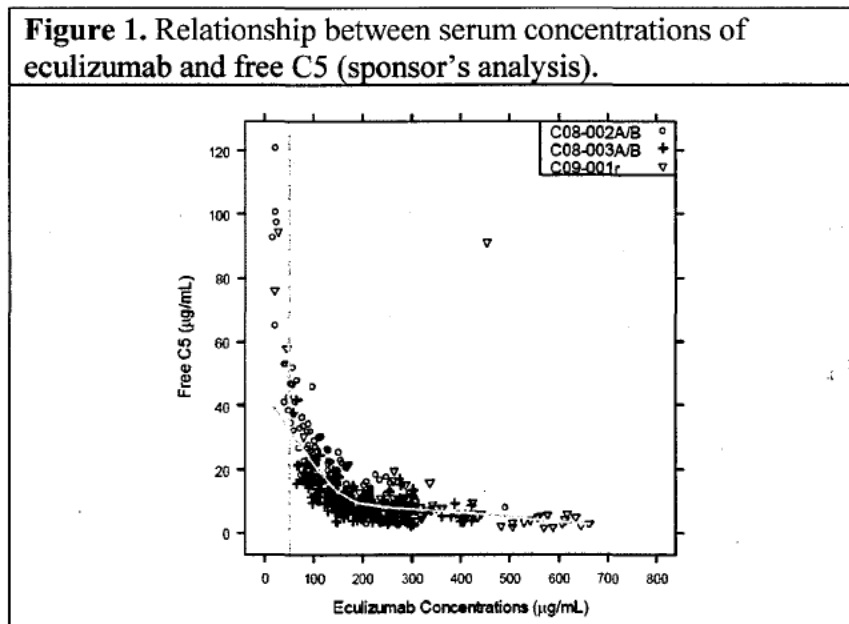


Table 3. Summary of simulated eculizumab trough concentrations following induction and maintenance doses.

Weight Category (n)	Median (Range) Trough Concentrations (µg/mL)	
	Induction	Maintenance
> 40 kg (43)	103.75 (43.41 -157.73)	170.2 (25.90 -310.43)
30- <40 kg (1)	117.8	242.98
20- <30 kg (5)	160.5 (129.07 -167.32)	199.57(133.35 -334.53)
10- <20 kg (4)	202.97 (150.83 - 262.84)	105.56 (34.35 -220.20)
5- <10 kg (4)	142.66 (134.60 -147.17)	66.87 (17.05 -235.15)

There were a total of eight endpoints used to assess the efficacy of eculizumab in clinical trials (**Table 4**). Due to the complex nature of the disease process, different endpoints were needed to assess the effect of the drug on the various manifestation of the aHUS disease process.

Table 4. Clinical endpoints used to support aHUS indication

Clinical Endpoints	Studies		
	C08-002A/B	C08-003A/B	C09-001r
Change in platelet count	Primary	X	X
TMA event-free status	X	Primary	X
TMA intervention rate	X	X	X
Change in renal function	X	X	X
Change in hemoglobin	X	X	X
QoL measures	X	X	X
Hematologic normalization	X	X	X
Complete TMA response	X	X	X

After consultation with the medical officer, Martha Donoghue, the following three endpoints were used for ER analysis:

- **TMA event-free status:** Absence of for at least 12 weeks: a decrease in the platelet count > 25% from the platelet count pre-PT baseline, PT and new dialysis
- **Change in renal function:** estimated GFR improvement > 15 mL/min
- **Hematological Normalization:** Normalization of platelet count and LDH levels in patients who had abnormal platelet counts at baseline or immediately prior to baseline. If no LDH measurement was reported during eculizumab treatment, the LDH criterion was waived.

For all ER analyses, model-predicted steady-state AUC (AUCss) was used. This was computed using patient's estimated clearance from the population PK model and the administered maintenance dose. This AUCss was consistent across weight groups as described in section 2.5. **Table 5** below shows calculated median and range of AUCss values for each AUCss quartiles used in the exposure-response analysis. For the induction portion of the dosing regimen, single dose simulated single dose AUCs were calculated (see section 5).

Table 5. Median and range of AUCss values for each AUC quartile.

Quartile	AUCss (mg*hr/L)		
	Median	Min	Max
1	56075	26432	68966
2	84507	70588	95238
3	106195	97561	113208
4	131868	117647	200000

In addition, for all ER analyses, response was determined by calculating the proportion of respondents and the associated binomial confidence intervals. ER relationship for the efficacy endpoints was not identified (**Figure 2**). Similarly the proportion of patients with TMA event free status, change in renal function, and hematologic normalizations were similar across different weight and age groups (**Figure 3** and **Figure 4**).

Figure 2. Proportion (95% CI) of responders vs. AUCss quartiles

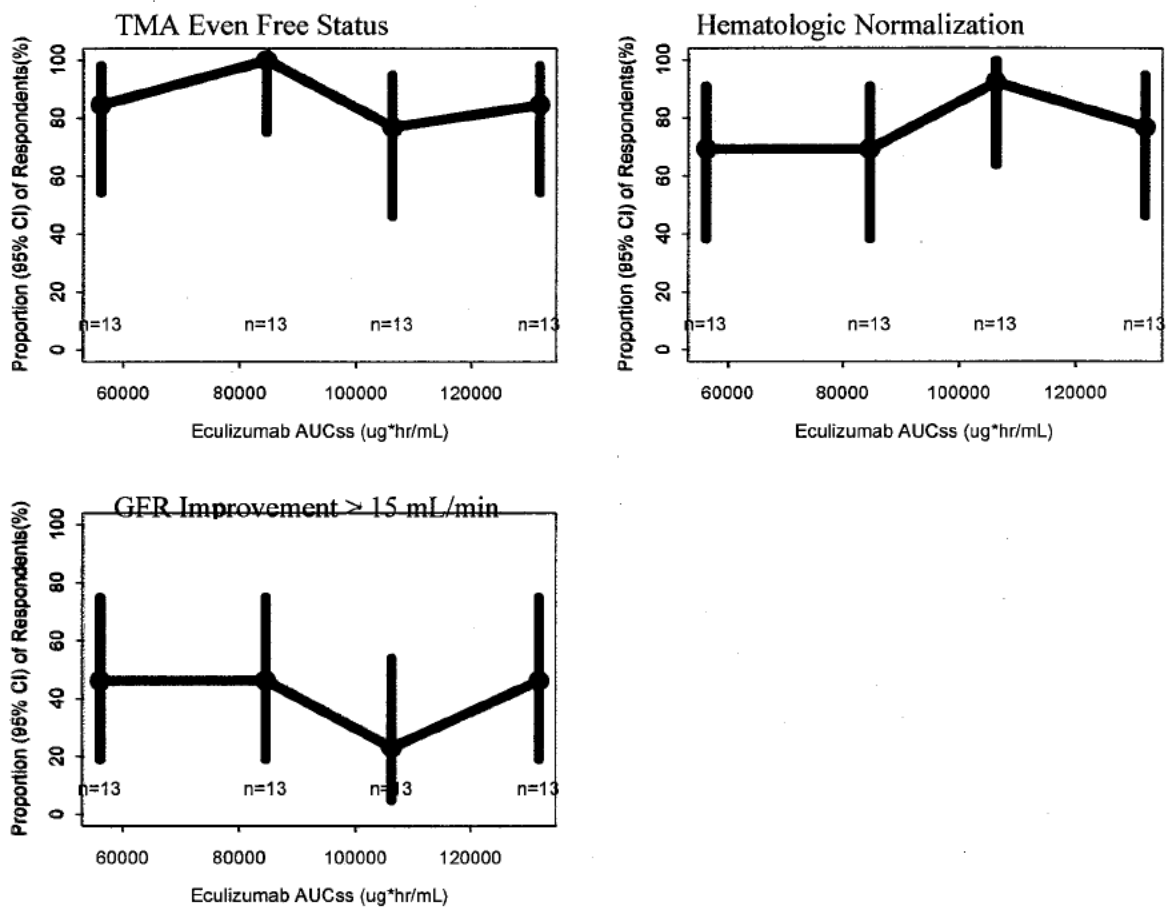


Figure 3. Proportion (95% CI) of responders vs. weight category

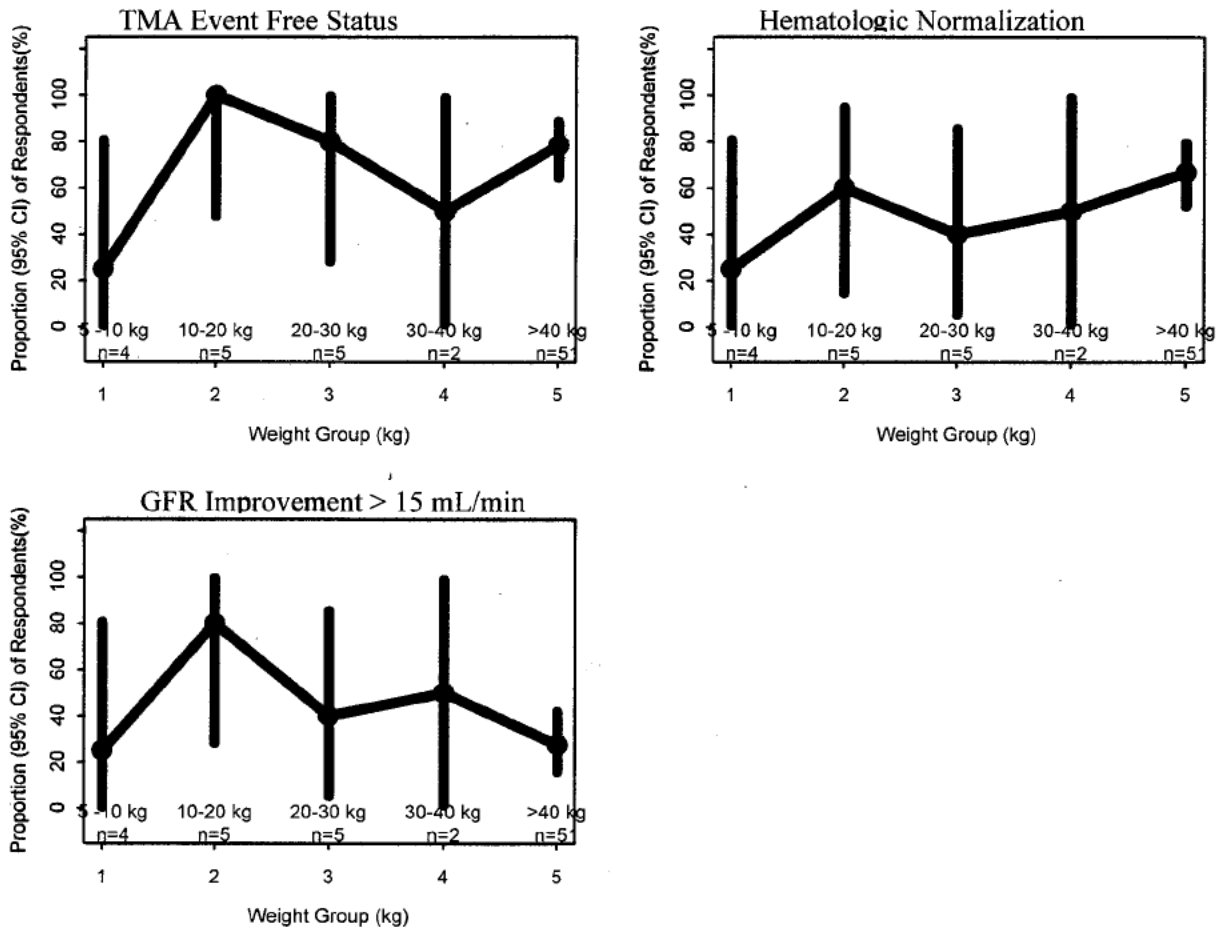
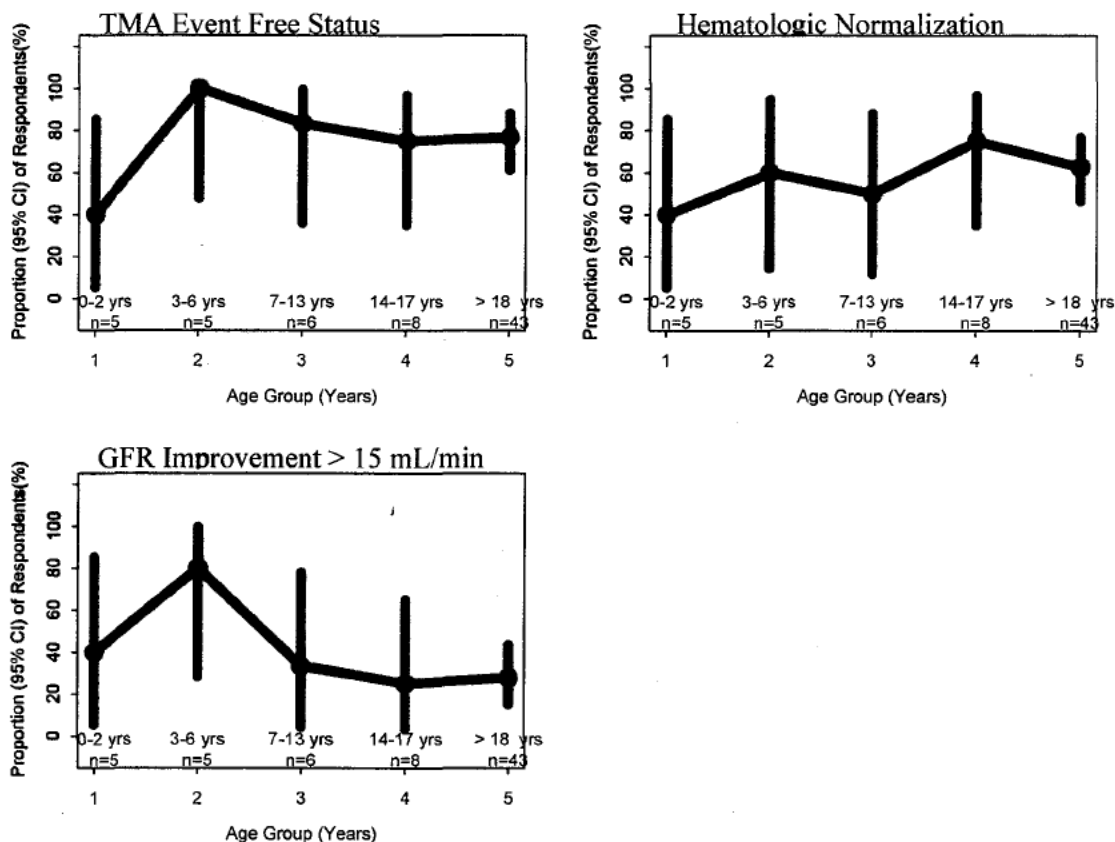


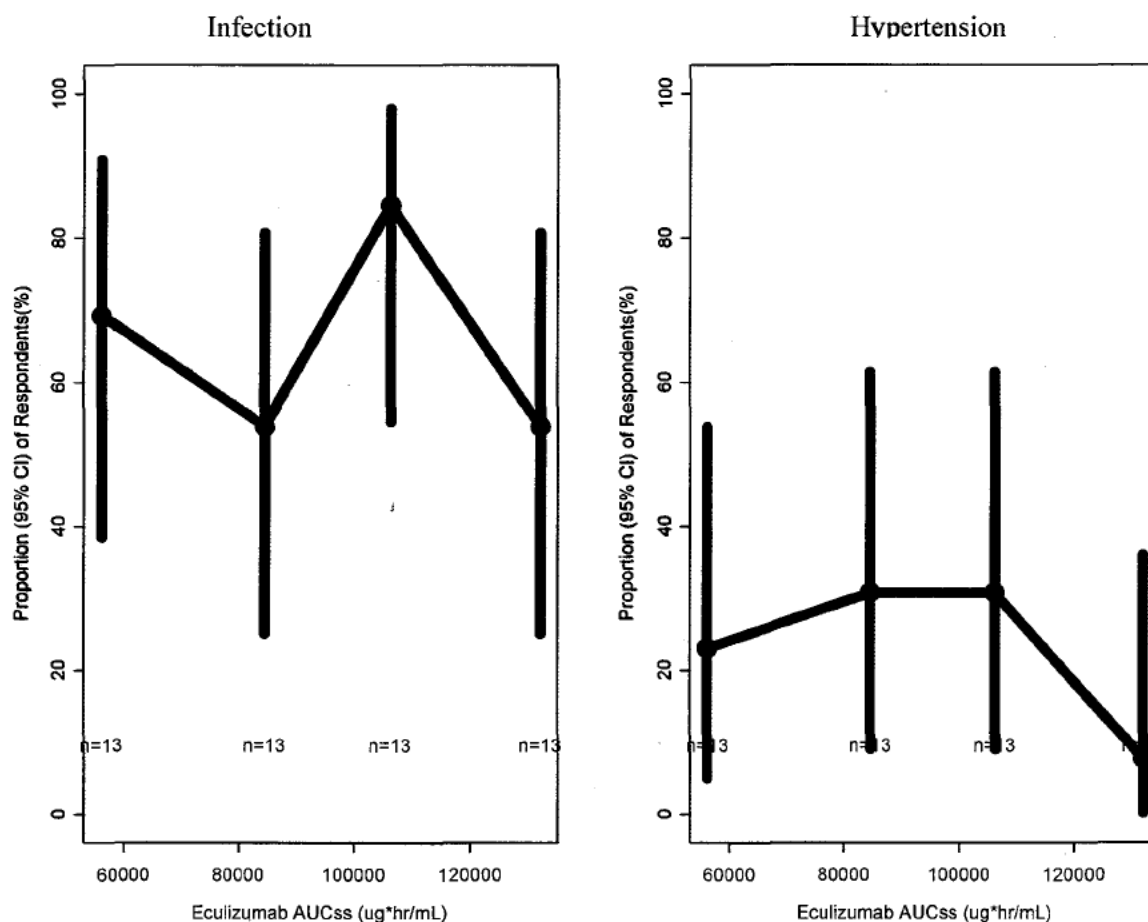
Figure 4. Proportion (95 % CI) of responders vs. age category



2.3.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Infections and hypertension were reported to be the most frequent adverse effects. In clinical trials, 63% of the patients had some type of infection while 19% of the patients had hypertension. ER analyses were performed to investigate whether the rates of infection and hypertension were related to the eculizumab exposure. **Figure 5** shows there is no relationship between AUCs and the proportion of patients with these adverse events.

Figure 5. Proportion (95% CI) of patients with infection hypertension vs. eculizumab AUCss.



2.3.3 Is the dose and dosing regimen selected consistent with the known ER relationship?

Predicted eculizumab AUC calculated using patients' clearance estimates along with administered and planned (per protocol doses) were consistent across weight groups (see section 2.4).

ER analysis for efficacy and safety support selecting dosing regimen for the following reasons:

- No exposure-response relationship for three of the clinical endpoints, which suggests that selected doses provide sufficient exposure in patients of varying size and age.
- Similarly, there is no exposure-response analysis for infection and hypertension. Since all studies were single arm trials, it is not clear whether the adverse events were results of disease progression or treatment by the drug.

2.4 WHAT ARE THE PK CHARACTERISTICS OF THE DRUG?

A population pharmacokinetics analysis was performed by the sponsor. A one-compartment PK model with first order elimination adequately described the data. Body weight was determined to

be a significant covariate on both clearance (CL) and volume (V) (Table 6). Body weight was incorporated into the model using allometric methodology. Final population PK parameter estimates are shown in Table 6. As shown on Figure 6, estimated clearance values increase with weight. However, this weight-clearance relationship was accounted for in the allometric scaling as shown by the lack of relationship between the inter-individual variability for clearance and weight (Figure 6).

The typical clearance and volume parameters of eculizumab, for a 70 kg adult patient, were estimated to be 0.0146 L/hr and 6.14 L, respectively. In patients with plasma intervention, the clearance of eculizumab was increased to 3.66 L/hr, reducing the half-life of eculizumab to 1.26 hours.

Table 6. Population PK parameter estimates of eculizumab.

Population PK Parameters^a	Prospective Studies^b (Prospective Population) (N=37)	Prospective and Retrospective Studies^c (Overall Population) (N=57)
Systemic Parameters		
CL (L/h) ^d	$CL = 0.0139 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.764}$	$CL = 0.0146 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.669}$
V _c (L)	$V_c = 5.95 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.143}$	$V_c = 6.14 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.722}$
Correlation between CL and V _c	45.8%	No correlation on the model
Between Subject Variability		
On CL	29.6%	33.9%
On V _c	25.3%	20.9%
Error Model		
Additive error (µg/mL)	0 Fix	23.0
Proportional error (%)	30.7	31.9

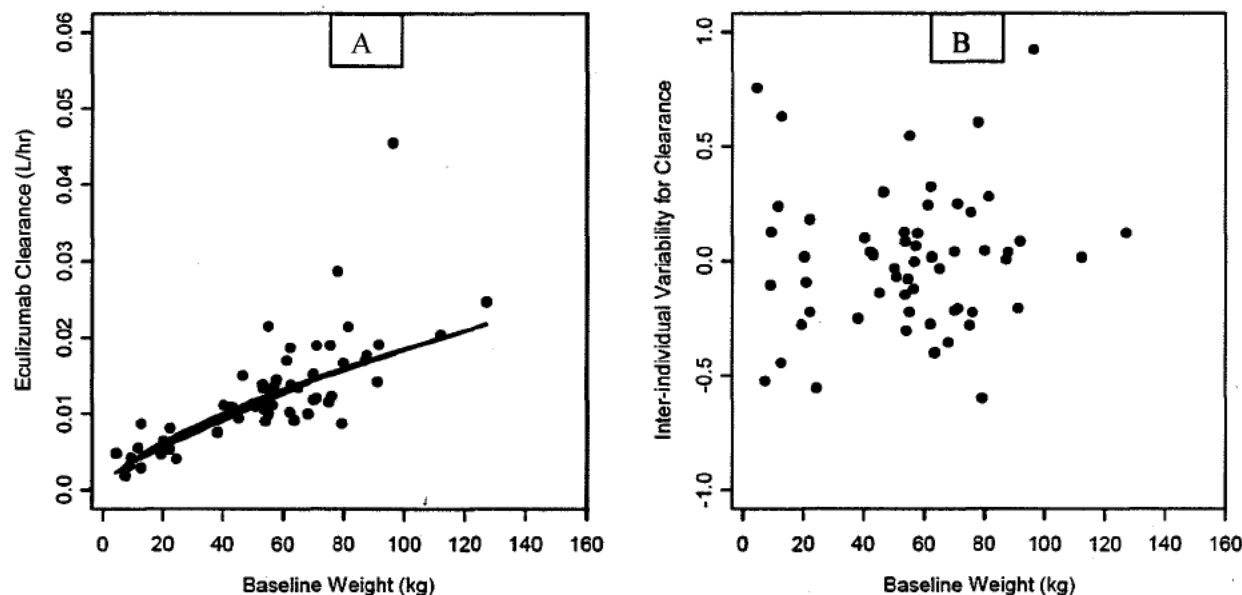
^a CL=Clearance of eculizumab; V_c = Volume of central distribution

^b Protocols C08-002A/B and C08-003A/B

^c Protocols C08-002A/B, C08-003A/B and C09-001r

^d The typical CL of eculizumab in the prospective and the combined studies were 3.35, and 3.66 L/h during the PE intervention, respectively.

Figure 6. Eculizumab clearance vs. weight (A) and inter-individual variability for clearance vs. weight (B)



2.5 INTRINSIC FACTORS

2.5.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

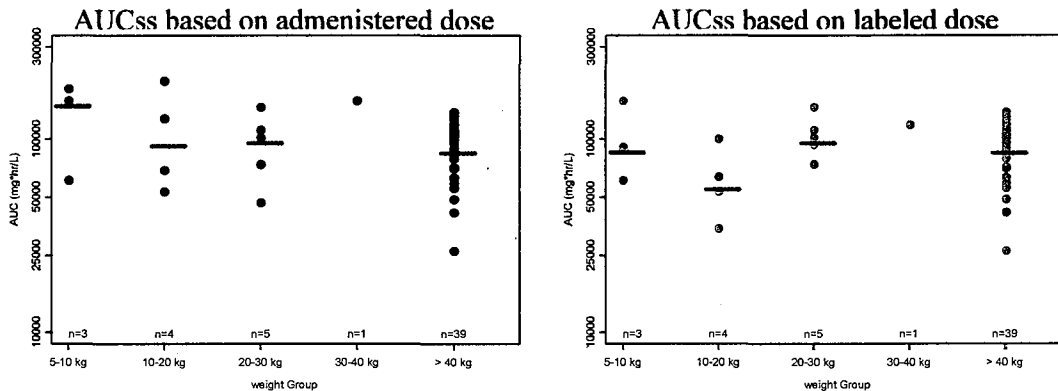
Based on population PK analysis, it was shown that the clearance and volume parameters of increased with weight. Instead of a weight-based (e.g., mg/kg) dose, the dose in children was determined based on weight cut-off values as described in section 2.1.3. **Table 7** summarizes mean clearance values for each weight category, showing an increasing trend of clearance with increasing weight. Consequently, the weight cut-off based doses of eculizumab results in similar AUC values across the different weight groups (**Figure 7**). AUCss values were calculated using administered and planned or labeled maintenance doses for each weight category.

Other covariates that were evaluated and found to have no effect on the PK of eculizumab included in the population PK analysis were age, race and disease type, gender, renal function, hepatic function and presence of auto-antibodies.

Table 7. Summary of clearance estimates for each weight category

Weight Group	N	Mean Clearance (L/hr)	SD
≥ 40 kg	43	0.015072	0.00653
30- <40 kg	1	0.007566	-
20- <30 kg	5	0.005999	0.001455
10- <20 kg	4	0.005488	0.002405
5- <10 kg	4	0.003602	0.001303

Figure 7. Mean (95% CI) of estimated AUC by weight category.



2.5.2 Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments, if any, are recommended for each group?

There was no ER relationship between eculizumab AUCss and clinical endpoints. Therefore, no dose adjustment recommendations are made.

2.5.3 Immunogenicity

2.5.3.1 *What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?*

Anti-eculizumab antibody samples were collected in studies C08-002 and C08-003 (n=37). Samples were collected at baseline, and trough samples on days 28, 84, 182, and every 26 weeks thereafter until the end of study. Additional samples were during the exit visit. One patient was shown to have anti-eculizumab antibody. There was no evidence of neutralization or intolerance in this patient as confirmed by the Neutralizing Anti-Drug Antibodies assay method.

2.5.3.2 *Does the immunogenicity affect the PK and/or PD of the therapeutic protein?*

The patient with anti anti-eculizumab antibody exited the study after the first dose due to diagnoses with systemic lupus erythematosus, therefore, the influence of immunogenicity on the PK eculizumab can not be determined based on available data.

2.5.3.3 *Do the anti-product antibodies have neutralizing activity?*

Neutralizing antibodies have not been detected in the subject who tested positive for anti-eculizumab antibodies.

2.5.3.4 *What is the impact of anti-product antibodies on clinical efficacy?*

The eculizumab immunogenicity incidence is low and was not associated with any clinical consequences.

2.5.3.5 *What is the impact of anti-product antibodies on clinical safety?*

No evidence of altered safety profiles has been observed in the subject who tested positive for anti-drug antibody.

2.6 EXTRINSIC FACTORS

2.6.1 **What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?**

Patients that had plasma extraction (PE) procedures were shown to have increased clearance of eculizumab to 3.6 L/hr, and decreased half life to 1.6 hours. No other extrinsic factors were shown to influence the PK of eculizumab. Supplemental eculizumab doses are recommended after episodes of plasma interventions.

2.7 ANALYTICAL SECTION

An ELISA method was validated for quantitative measurement eculizumab in human serum. The assay performances are described below:

Validated concentration range: 9.4 to 600 µg/mL

Assay precision (%CV): < 20%

Assay accuracy: recovery value of $100 \pm 25\%$ of the known concentration in that sample

Of note is that, although the upper limit of the validated assay concentration range is 600 µg/mL, few patients in the retrospective study had concentrations > 600 mg/mL. Therefore, reported eculizumab concentrations values > 600 mg/mL may not be accurate. However, the assay's inability to accurately characterize concentrations > 600 mg/mL is not expected to have meaningful clinical consequence.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included.

6.2 Immunogenicity

As with all proteins there is a potential for immunogenicity. 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 molecular as target was used for the aHUS indication. Low titers of antibodies to Soliris were detected in 3/196 (2%) of all PNH patients treated with Soliris by the ELISA assay. In patients with aHUS treated with Soliris, antibodies to Soliris were detected in 1/37 (2.7%) by the ECL assay. An ECL based neutralizing HAHA assay with (b) (4) sensitivity was performed to detect neutralizing antibodies for the 37 patients with aHUS. No neutralizing activity to Soliris was detected in patients with aHUS treated with Soliris. No apparent correlation of antibody development to clinical response was observed in both indications. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Soliris in an ELISA based assay and/or an ECL based assay are highly dependent on the sensitivity and specificity of the assay used. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to Soliris with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No drug-drug interaction trials have been conducted with Soliris.

8 USES IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of Soliris for the treatment of PNH in pediatric patients below the age of 18 years have not been established.

Three clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS included a total of 25 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 Dosage and Administration (2.2), 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)].*

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

A population PK analysis with a standard 1-compartmental model was conducted on the multiple dose PK data from 40 PNH patients receiving the recommended Soliris regimen [see *Dosage and Administration (2.1)*]. In this model, the clearance of Soliris for a typical PNH patient weighing 70 kg was 22 mL/hr and the volume of distribution was 7.7 L. The half-life was 272 ± 82 hrs (mean $\pm$ SD). The mean observed peak and trough serum concentrations of Soliris by week 26 were 194 ± 76 mcg/mL and 97 ± 60 mcg/mL, respectively.

A second population PK analysis with a standard 1 compartmental model was conducted on the multiple dose PK data from 57 aHUS patients receiving the recommended Soliris regimen in studies 1, 2 and 3. In this model, the clearance of Soliris for a typical aHUS patient weighing 70 kg was 14.6 mL/hr and the volume of distribution was 6.14 L. The elimination half-life was 291 h (approximately 12.1 days).

The clearance and half-life of eculizumab were also evaluated during plasma exchange interventions. Plasma exchange increased the clearance of eculizumab to 3660 mL/hr and reduced the half-life to 1.26 hours. Supplemental dosing is recommended when Soliris is administered to aHUS patients receiving plasma infusion or exchange [see *Recommended Dosage Regimen (2.1)*].

Studies have not been conducted to evaluate the PK of Soliris in special patient populations identified by gender, race, age (pediatric or geriatric), or the presence of renal or hepatic impairment. Pediatric and adolescent patients (less than 18 years of age) and patients with renal impairment were included in the aHUS clinical studies [see *Clinical Studies (14)*]. Population PK analysis showed age, gender, race, and renal function do not influence the PK of eculizumab.

4 APPENDICES: REVIEWERS COMMENTS ON THE SPONSOR'S PK ANALYSIS

The sponsor's population PK conclusions are summarized below:

- Results from the current population PK analysis suggest that the proposed dosing regimens for aHUS patients across all age groups, and body weight groups resulted in concentrations within the therapeutic range of the product.
- PK/PD modeling further supported the proposed dosing regimen since eculizumab concentrations displayed close-to-full inhibition of percentage and reduction in free C5 in aHUS patients
- The adults and children weighting ≥ 40 kg receive flat eculizumab dose while children weighing less than 40 kg receive eculizumab doses based on weight cut-off.

Reviewer's comments:

Sponsor's population PK analysis is adequate in characterizing eculizumab PK data. Body weight was appropriately identified as a covariate that explained the interindividual variability eculizumab PK.

However, we differ with the sponsor's conclusion as follows:

The sponsor did not provide sufficient emphases to one of the significant covariates, plasma intervention.

5 SYNOPSIS OF SPONSOR'S ANALYSIS

Note: Because the sponsor did not provide synopsis of the population PK analysis. The results section of the population PK analysis report is attached.

**POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS**

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RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS**

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POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

2.1. Population PK Modeling of Prospective (C08-002A/B and C08-003A/B) and Retrospective (C09-001r) Data in aHUS Patients

2.1.1. aHUS Patients - Demographic Data in Pooled Studies

Table 1: aHUS Patients Demographic Data - Categorical Data

Variables	Count (%) ^a		
	Categories ^b	C09-001r (N=20)	Prospective and Retrospective Studies ^c (N=57)
Sex	Male	10 (50.0%)	23 (40.4%)
	Female	10 (50.0%)	34 (59.6%)
Race	Caucasian	14 (70.0%)	46 (80.7%)
	Asian	1 (5.0%)	2 (3.5%)
	Black	2 (10.0%)	5 (8.8%)
	Other	3 (15.0%)	4 (7.0%)
Patient Disease Setting Group	Missing	20 (100%)	20 (35.1%)
	PT-chronic	0 (0%)	20 (35.1%)
	PT-resistant	0 (0%)	17 (29.8%)
Plasma Intervention While on Eculizumab Treatment	FFP	One patient had 6 interventions and another had 3 interventions (10%)	One patient had 6 interventions and another had 3 interventions (3.5%)
	PE	One patient had 5 interventions and another had one intervention (10.0%)	Two patients had 5 interventions and another had one intervention (5.3%)
	PPH	0 (0%)	One patient had 8 interventions (1.8%) ^d
	none	18 (90.0%)	53 (93.0%)

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
 RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Table 1: aHUS Patients Demographic Data - Categorical Data (Continued)

Variables	Count (%) ^a		
	Categories ^b	C09-001r (N=20)	Prospective and Retrospective Studies ^c (N=57)
Human Anti-Human Antibody Immunogenicity	Missing	20 (100%)	20 (35.1%)
	Presence	0 (0%)	1 (1.8%)
	Absence	0 (0%)	36 (63.2%)
Complement factor mutations	Negative	10 (50.0%)	20 (35.1%)
	Positive	10 (50.0%)	37 (64.9%)
Kidney	Native	15 (75.0%)	37 (64.9%)
	Transplant	5 (25.0%)	20 (35.1%)
Antihypertensive Agents at Baseline	Presence	10 (50.0%)	25 (43.9%)
	Absence	10 (50.0%)	32 (56.1%)
Erythrocyte Stimulating Agents at Baseline	Presence	16 (80.0%)	38 (66.7%)
	Absence	4 (20.0%)	19 (33.3%)
Immunosuppressive Agents at Baseline	Presence	6 (20.0%)	21 (36.8%)
	Absence	14 (80.0%)	36 (63.2%)

^a N= Number of patients

^b FFP= Frozen fresh plasma; PE= Plasma exchange; PPH= Plasmapheresis; PT = Plasma Therapy

^c Protocols C08-002A/B, C08-003A/B and C09-001r

^d Intervention for patient in study C08-002A/B occurred after PK blood samples and after patient discontinued from the study.

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
 RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Table 2: aHUS Patients Demographic Data - Continuous Data at Baseline

Variables ^a	Mean (CV%) ^b Median[Range]	
	C09-001r (N=20)	Prospective and Retrospective Studies ^c (N=57)
Age (years)	12.7 (122%) 6.60 [0.221 – 51.5]	25.7 (67.6%) 24.2 [0.221 – 69.0]
Weight (kg)	29.0 (74.4%) 21.5 [4.40 – 77.7]	54.7 (50.2%) 56.2 [4.40 – 127]
Serum creatinine (µmol/L)	248 (109%) 143 [12.4 – 968]	293 (80.7%) 234 [12.4 – 968]
eGFR (mL/min/1.73m ²)	42.7 (106%) 26.6 [5.11 – 162]	31.8 (96.3%) 22.0 [4.97 – 162]
Hemoglobin (g/L) ^d	94.5 (18.1%) 95.0 [62.0 – 134.0]	97.6 (18.0%) 95.5 [62.0 -134]
Hemoglobin free in plasma (mg/dL) ^e	NA/NC	7.32 (115%) 5.10 [0.750 – 47.2]
Hematocrit (%) ^f	0.280 (17.6%) 0.278 [0.183 – 0.380]	0.292 (19.5%) 0.290 [0.183 – 0.420]
ALT (U/L) ^g	48.1 (214%) 20.0 [4.00 – 388]	34.8 (170%) 19.5 [4.00 – 388]
AST (U/L) ^e	88.5 (216%) 29.0 [7.00 – 716]	42.7 (233%) 23.5 [7.00 – 716]
Albumin (g/L) ^h	34.0 (21.9%) 34.0 [23.0 – 48.0]	38.2 (16.5%) 40.0 [23.2 – 48.0]
Bilirubin (µmol/L) ^g	11.7 (94.8%) 6.80 [1.71 – 32.5]	9.05 (72.4%) 6.84 [1.71 -32.4]

^a eGFR= Estimated glomerular filtration rate; ALT= Alanine aminotransferase; AST=Aspartate aminotransferase
^b CV= Coefficient of variation; NA= Not available; NC= Not calculated; N= Number of patients; CV= Coefficient of variation
^c Protocols C08-002A/B, C08-003A/B and C09-001r
^d One patient in study C09-001r had missing value
^e Only patients in studies C08-002A/B and C08-003A/B were included in the descriptive statistics.
^f 2 patients in study C09-001r had missing value.
^g 7 patients in study C09-001r had missing value.
^h 4 patients in study C09-001r had missing value.

**POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS**

2.1.2. Eculizumab Population PK Model – Pooled Studies

2.1.2.1. Eculizumab – Time Imputation and Exclusion for the Study C09-001r

Some imputations on the retrospective data were done based on these rules:

1. If the infusion start time was known, but the infusion end time was missing, the infusion duration was set to 35 minutes.
2. If both the infusion start and end times were unknown (but the infusion date was known), the infusion start time was set to 10:00 am unless an infusion at this time was incompatible with a trough or peak PK measurement on the same day. If a trough measurement occurred after 10:00 am on the same day, the infusion start time was set to the time of the trough PK measurement. If both a trough and a peak measurement were taken on the same day (patient 017-019 only), the infusion start time was set to the time of the trough PK measurement. The infusion duration was set to 35 minutes.
3. If the time of a PK measurement was missing, it was set to 1:00 pm unless this was deemed incompatible with an infusion and/or another PK measurement on the same day. If the PK measurement was a trough, the PK time was set to 1:00 pm if the infusion started later than 1:00 pm, and to the infusion start time otherwise. If the PK measurement was a peak, the PK time was set to 1:00 pm if the infusion ended before 12:00 pm, and to one hour after the end of infusion otherwise.
4. For patient 120-008, the PK times were missing but the time-points were named in hours/days post dose. For this patient, the PK times were set as follows: start of infusion for "Pre-dose", 1 hour after end of infusion for "1 hr post", 24 hours after end of infusion for "24 hrs post", 1:00 PM for "8 days post" and "19 days post".
5. For patient 012-003, two PK measurements were excluded: (1) pre-dose measurement with non-BLQ result on 01-07-2009 at 3:35 am; (2) trough measurement at 12:55 on 21-07-2009 (inconsistent with a dose at 10:00 AM on the same day).
6. Patient 212-017 had 10 weeks between the first two doses. Observed concentrations during this period were not included in the analysis. They were flagged.

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Table 3: Eculizumab –Effect of Retrospective and Prospective Studies on PK Parameters – Pooled Data

Parameter ^a	Covariates	MOF	ΔMOF	Estimate ^b	BSV (CL)	BSV (V _c)	p-value
Base model	PE on CL WT on CL and V _c	5282.931	---	---	33.91%	20.86%	---
Study on CL		5280.352	-2.579	1.3	33.62%	21.07%	0.108
Study on V _c		5281.096	-1.835	0.861	34.06%	19.82%	0.176
Study on CL and V _c		5278.178	-4.753	0.85	33.62%	19.92%	0.093
Note: Prospective studies (C08-002A/B and C08-003A/B) were regrouped.							

^a BSV= Between-subject variability; CL= Clearance of eculizumab; MOF= Minimum objective function; ΔMOF= Difference between the MOF value for the tested model and the base model; PE= Plasma exchange; V_c= Volume of central distribution of eculizumab; WT= Body weight at baseline

^b Multiplicative factor

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Table 4: Eculizumab – Population PK Parameters – Pooled Data

Population PK Parameters ^a	Prospective ^b Studies	Prospective and Retrospective Studies ^c
Systemic Parameters		
CL (L/h) ^d	$CL = 0.0139 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.764}$	$CL = 0.0146 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.669}$
V _c (L)	$V_c = 5.95 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.143}$	$V_c = 6.14 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.722}$
Correlation between CL and V _c	45.8%	No correlation
Between Subject Variability		
On CL	29.6%	33.9%
On V _c	25.3%	20.9%
Error Model		
Additive error (µg/mL)	0 Fix	23.0
Proportional error (%)	30.7	31.9

^a CL=Clearance of eculizumab, PE= Plasma exchange, V_c= Volume of central distribution of eculizumab.

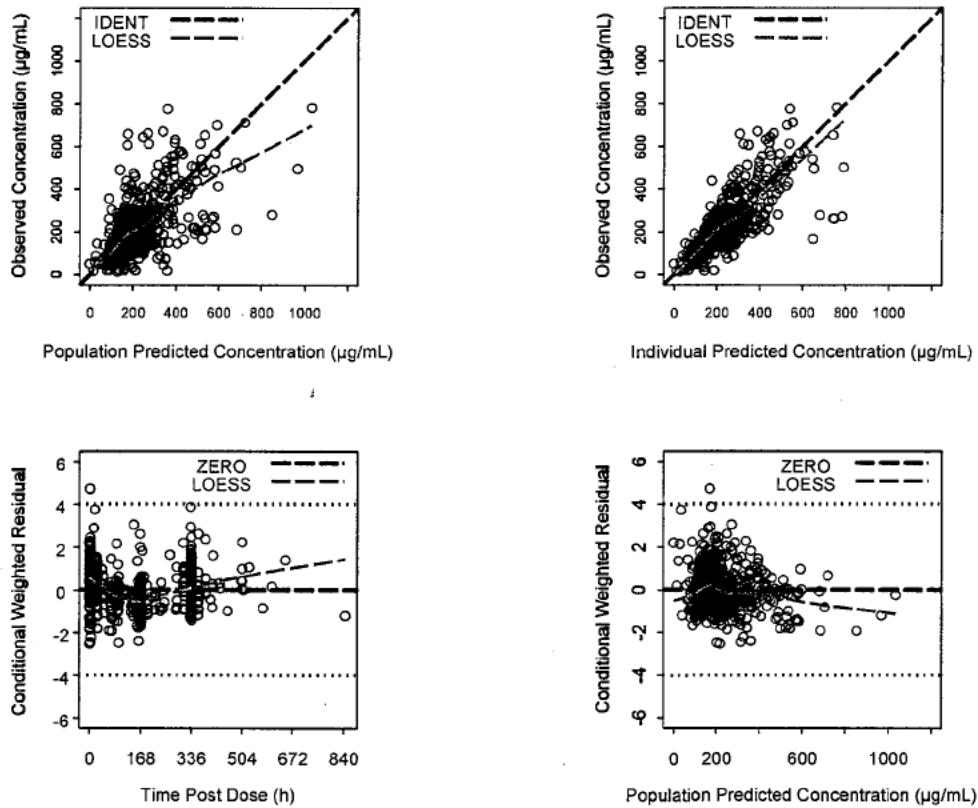
^b Protocols C08-002A/B and C08-003A/B

^c Protocols C08-002A/B, C08-003A/B and C09-001r

^d When aHUS patients undergo plasma exchange, CL of eculizumab in the prospective study was 3.35 L/h during the PE intervention. When combining the prospective and retrospective studies, CL of eculizumab was 3.66 L/h during the PE intervention

**POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS**

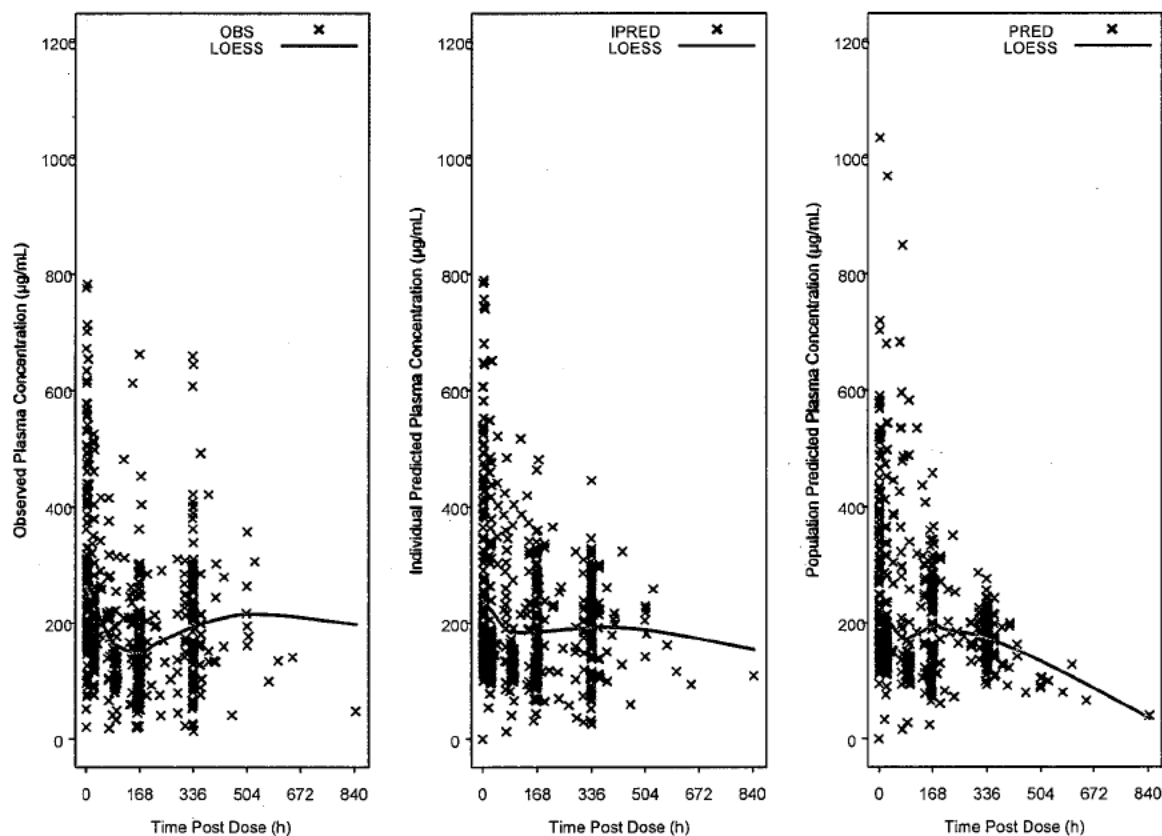
**Figure 1: Eculizumab Population PK Model Discrimination – Goodness-of-Fit –
Pooled Data**



LOESS= Locally weighted scatterplot smoothing; IDENT= Identity line.

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Figure 2: Eculizumab Population PK Model Discrimination – Observed, Individual and Population Predicted Concentrations versus Time Post Dose – Pooled Data

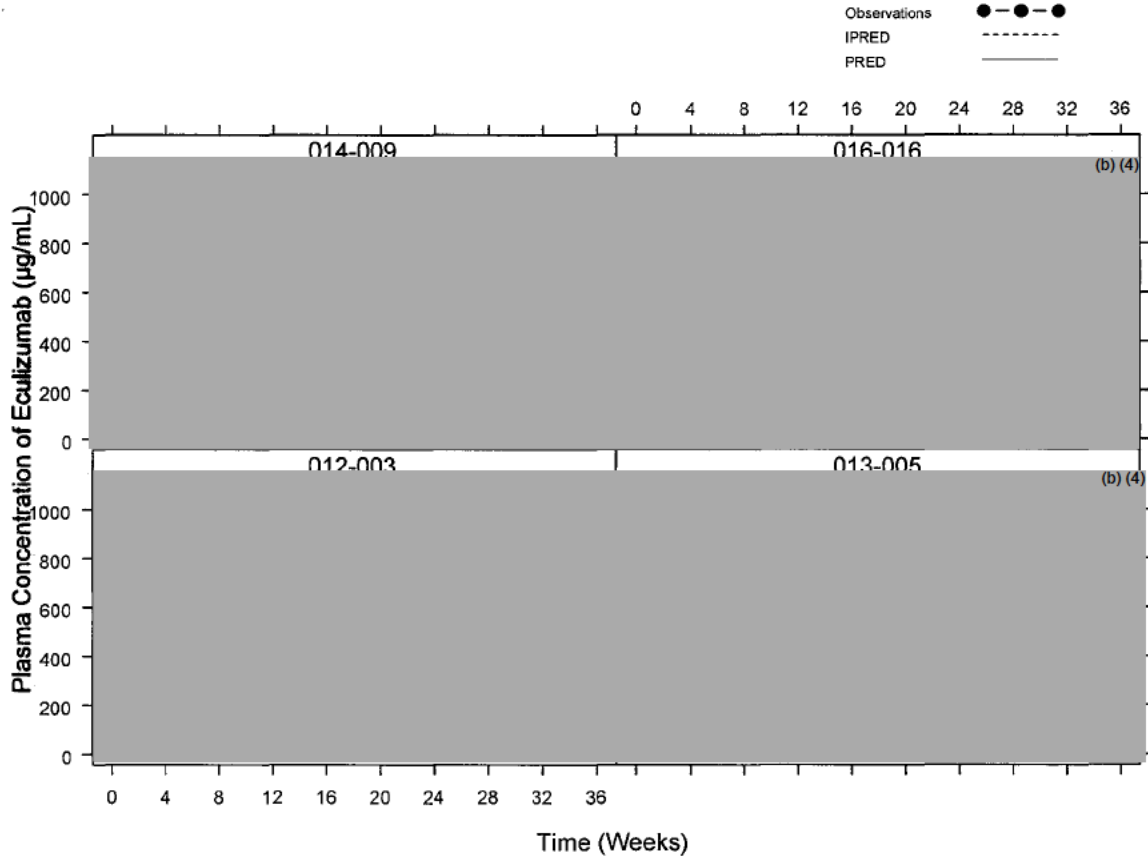


IPRED= Individual predicted concentration; LOESS= Locally weighted scatterplot smoothing; OBS= Observed concentration; PRED= Population predicted concentration

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

2.1.3. Eculizumab – Individual Time-Profiles

Figure 3: Eculizumab – Individual Time-Profiles –Study C09-001r

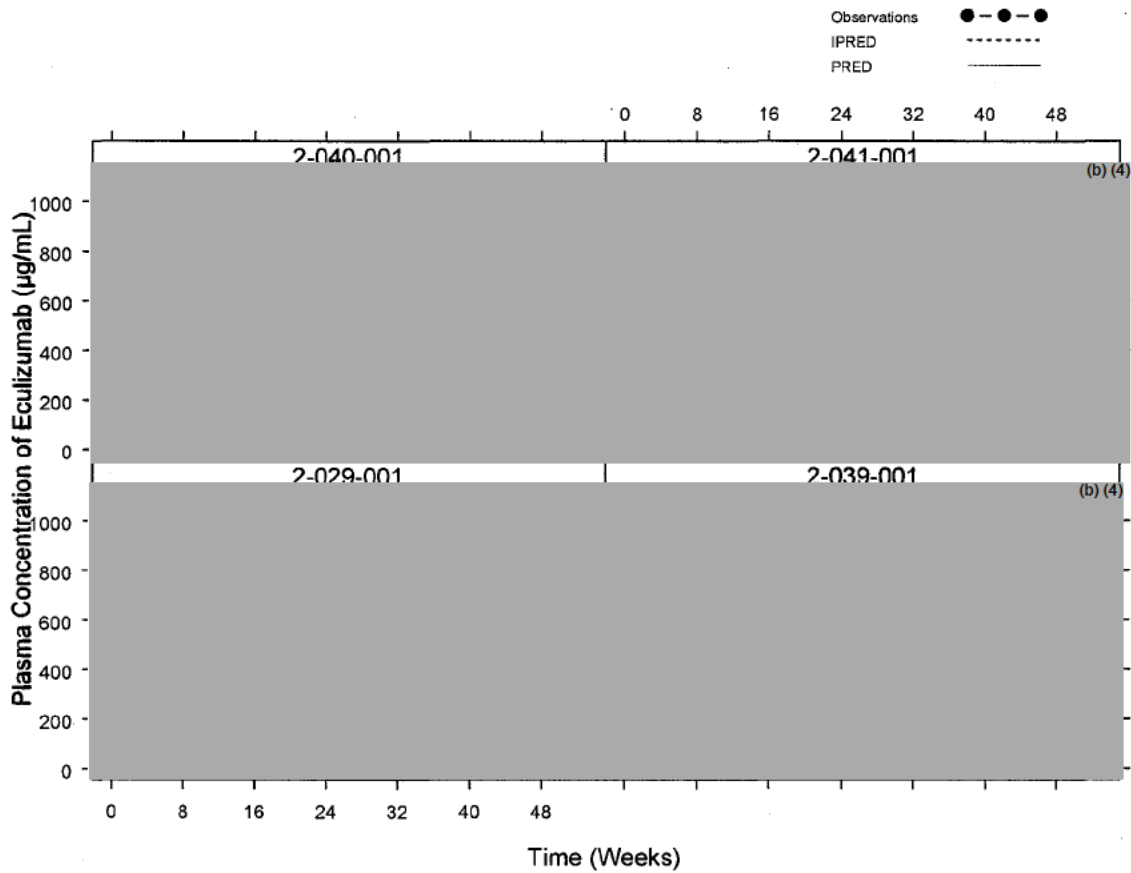


IPRED= Individual predicted concentration; PRED= Population predicted concentration
Dotted lines represent the target window for eculizumab concentrations

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POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Figure 4: Eculizumab – Individual Time-Profiles –Study C08-002A/B

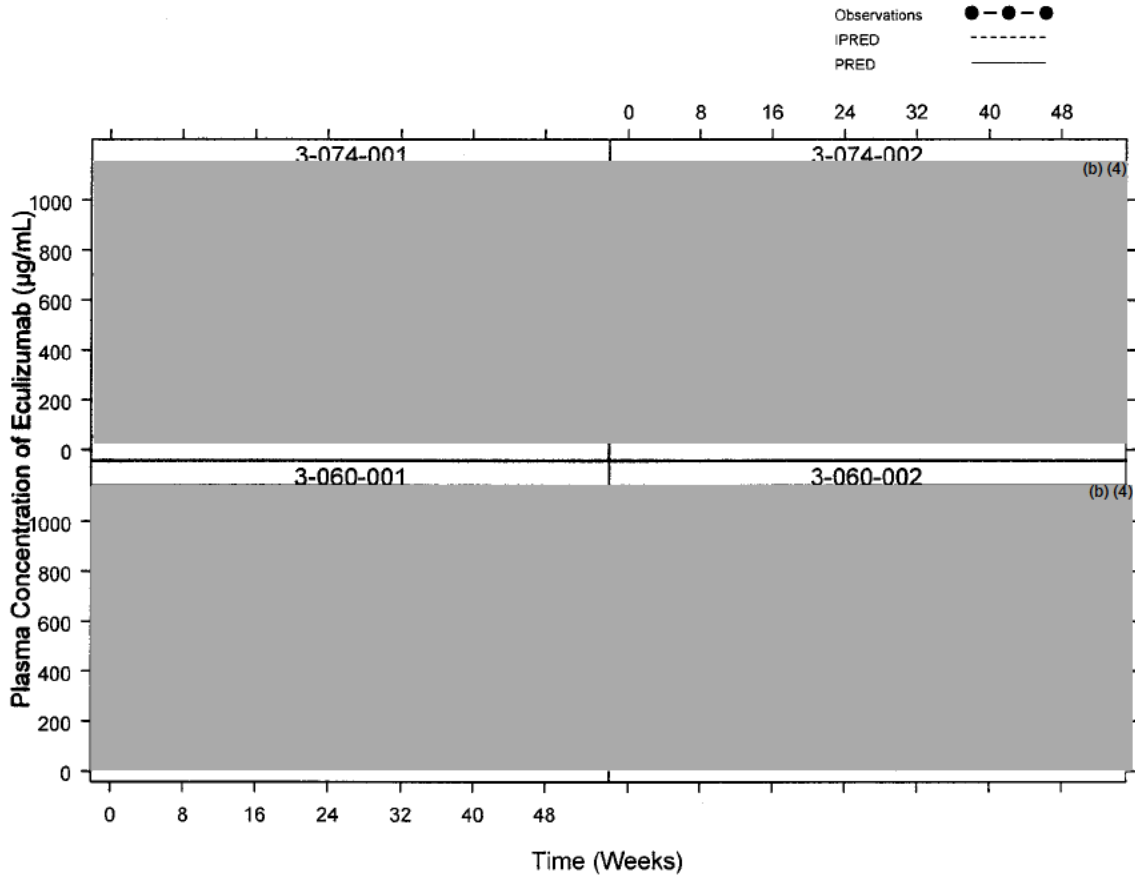


IPRED= Individual predicted concentration; PRED= Population predicted concentration
Dotted lines represent the target window for eculizumab concentrations

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POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Figure 5: Eculizumab – Individual Time-Profiles –Study C08-003A/B



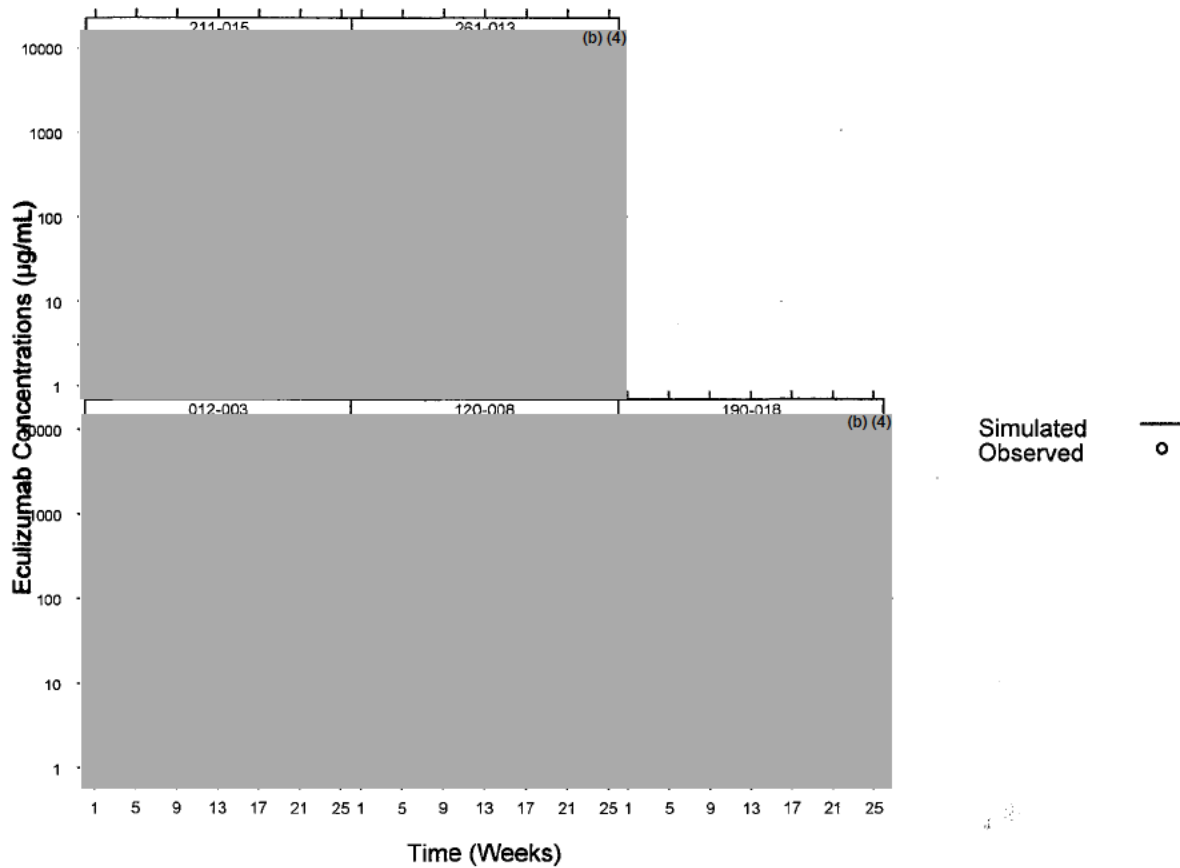
IPRED= Individual predicted concentration; PRED= Population predicted concentration
Dotted lines represent the target window for eculizumab concentrations

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POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

2.1.4. Simulated and Observed Individual Time Profiles of Eculizumab Concentrations for aHUS Patients in Retrospective (C09-001r) Study

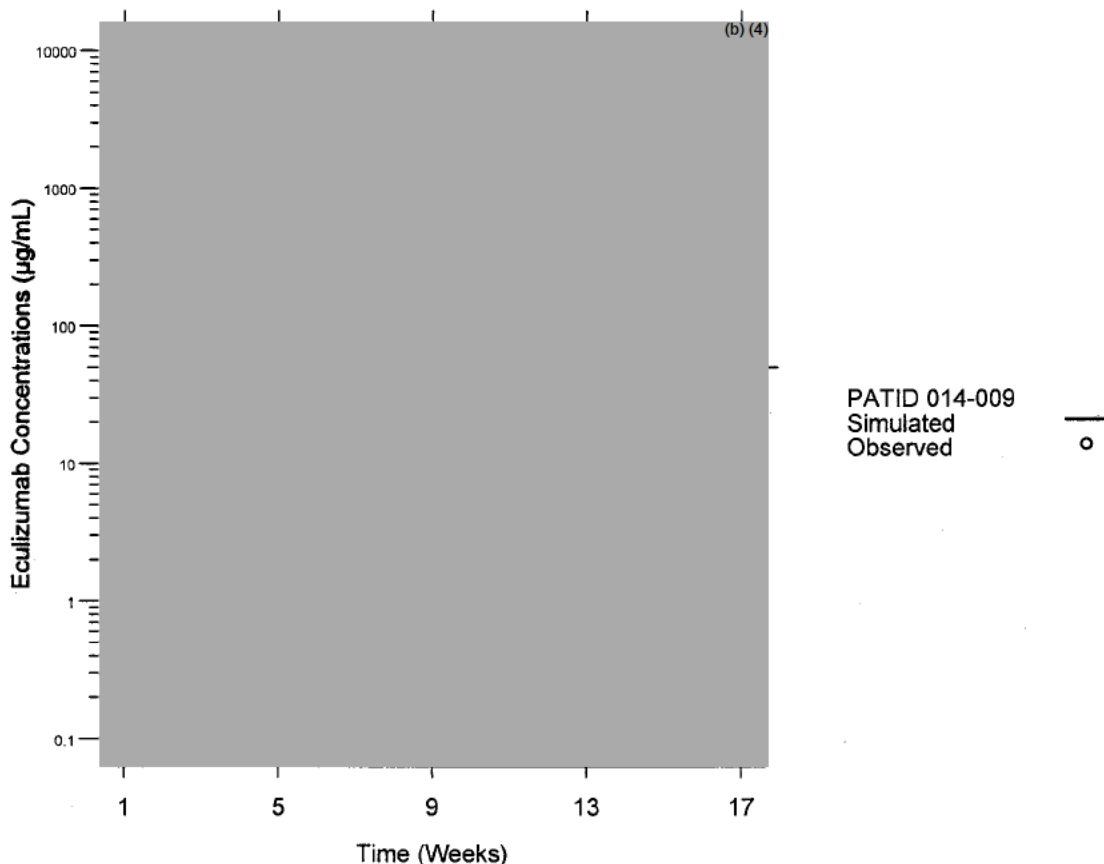
Figure 6: Simulated and Observed Individual Time Profiles of Eculizumab Concentrations for aHUS Patients in Retrospective (C09-001r) Study with Body Weight ≥ 40 kg



Note: Simulated concentrations were derived with the 900 mg weekly x4 following by 1200 mg week 5, 1200 mg Q2 weeks
Red lines represent the target window for eculizumab concentrations

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Figure 7: Simulated and Observed Individual Time Profiles of Eculizumab Concentrations for aHUS Patients in Retrospective (C09-001r) Study with Body Weight ≥ 40 kg Receiving PE -- Without Extra Dose of 600 mg After PE

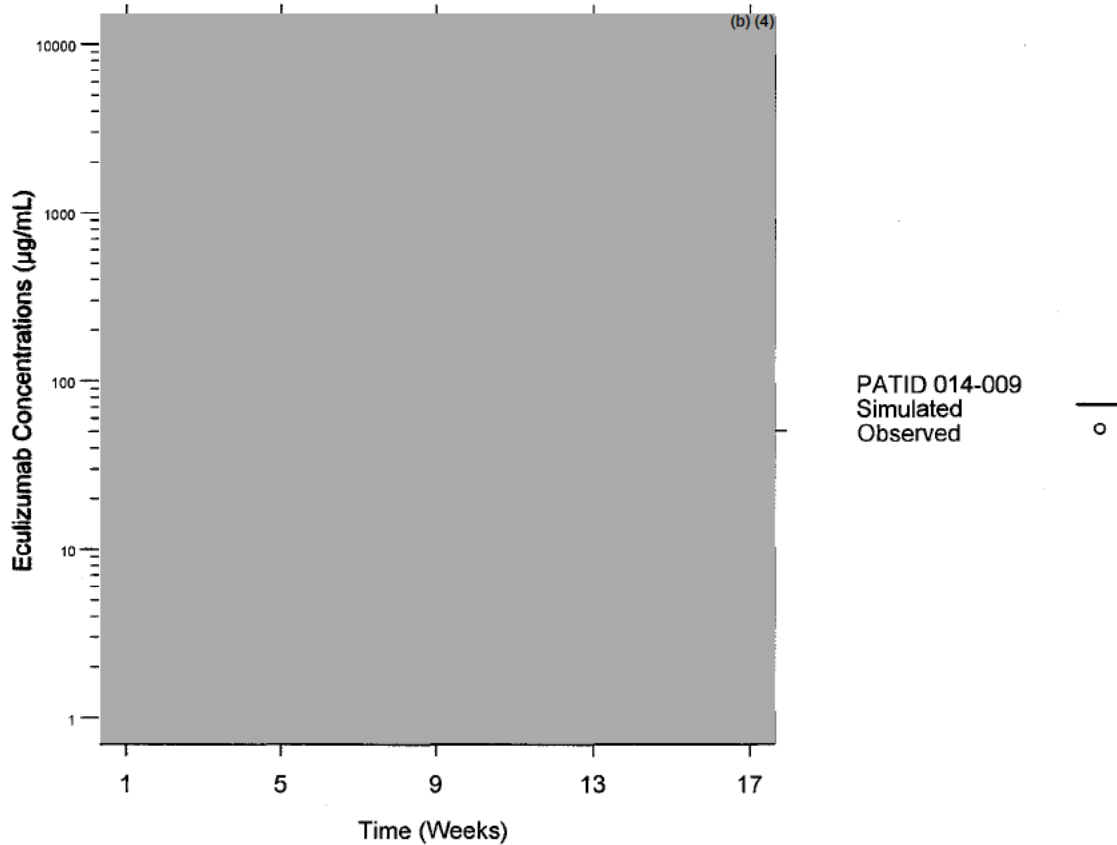


Note: Simulated concentrations were derived with the 900 mg weekly x4 following by 1200 mg week 5, 1200 mg Q2 weeks

Red lines represent the target window for eculizumab concentrations

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

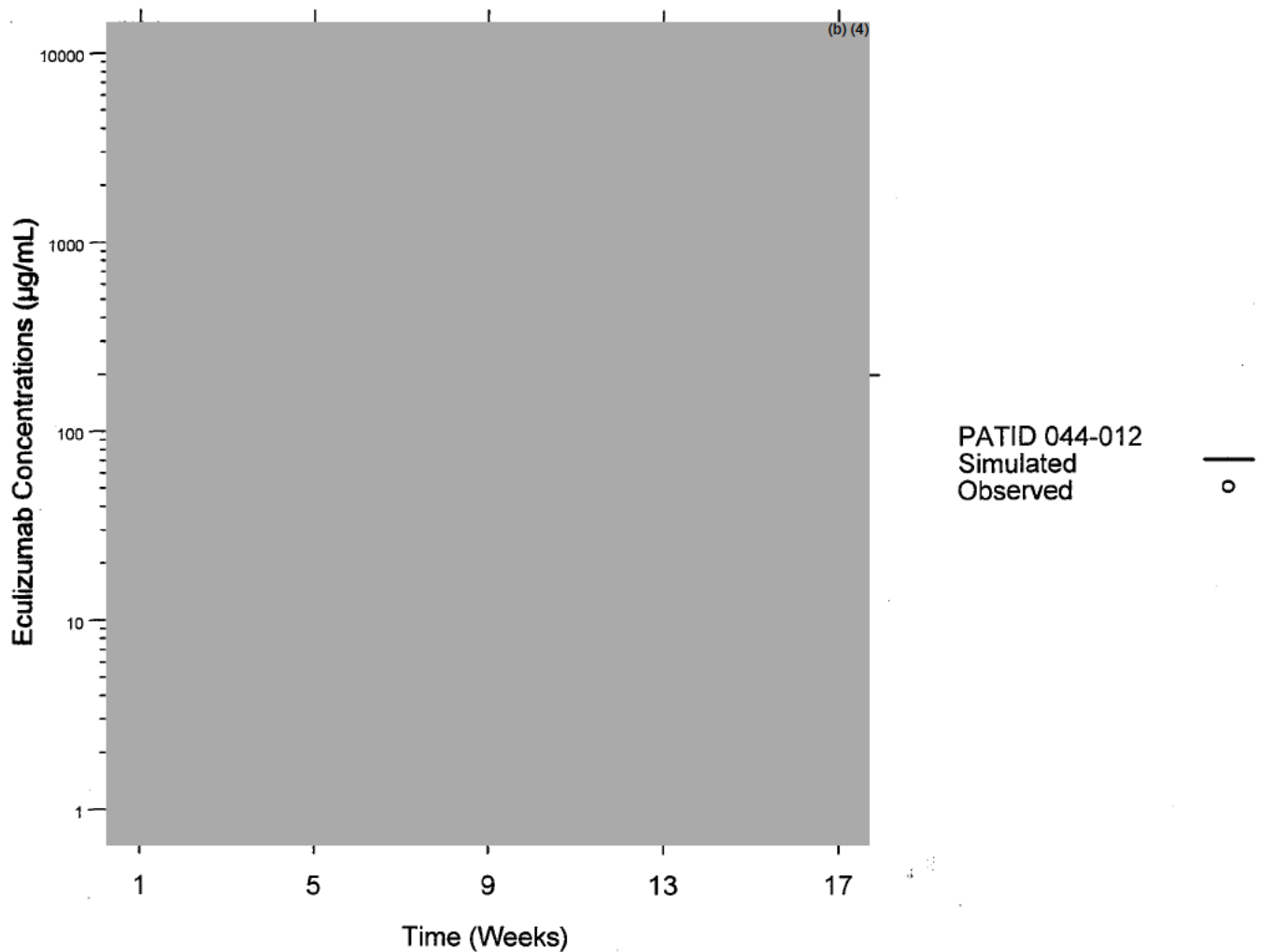
Figure 8: Simulated and Observed Individual Time Profiles of Eculizumab Concentrations for aHUS Patients in Retrospective (C09-001r) Study with Body Weight ≥ 40 kg Receiving PE -- With Extra Dose of 600 mg After Each PE



Note: Simulated concentrations were derived with the 900 mg weekly x4 following by 1200 mg week 5, 1200 mg Q2 weeks
Red lines represent the target window for eculizumab concentrations

**POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS**

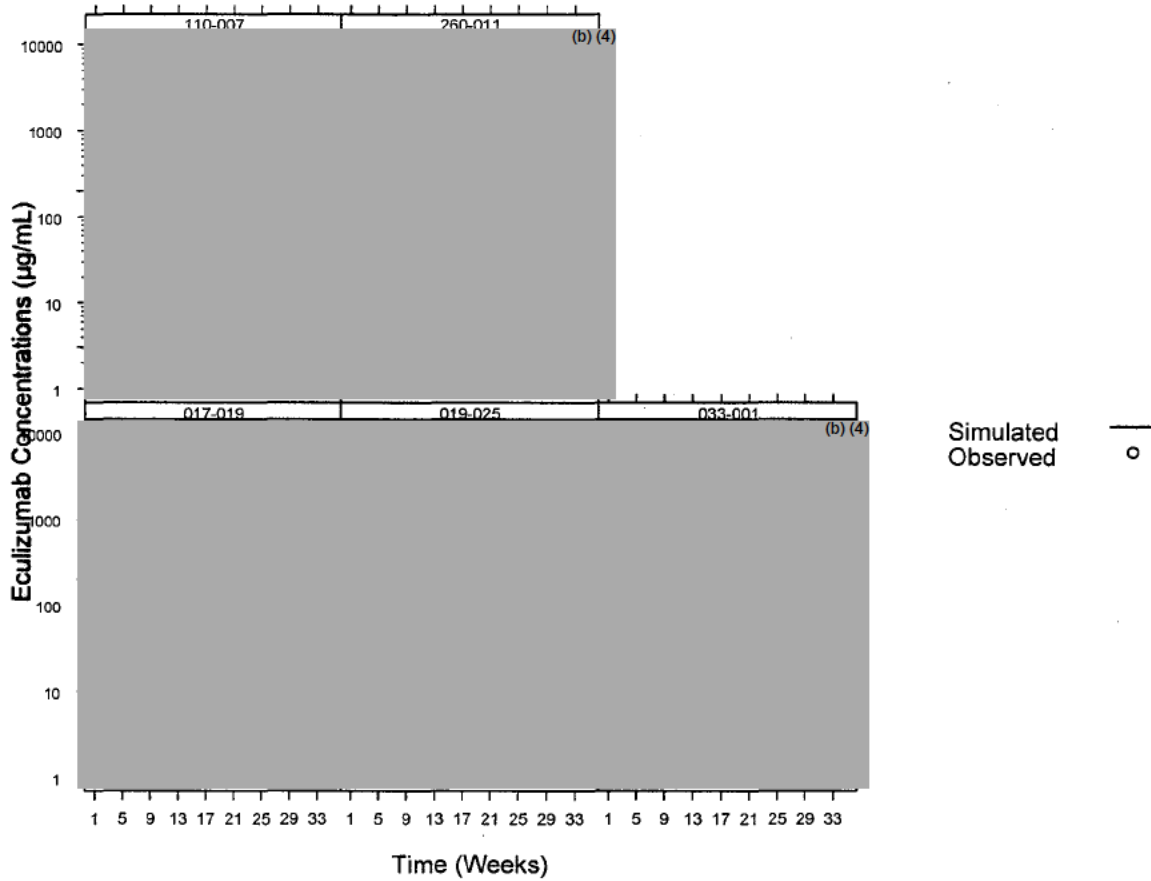
**Figure 9: Simulated and Observed Individual Time Profiles of Eculizumab
Concentrations for aHUS Patients in Retrospective (C09-001r) Study with
Body Weight 30 to <40 kg**



Note: Simulated concentrations were derived with the 600 mg weekly x2 following by 900 mg week 3, 900 mg Q2 weeks
Red lines represent the target window for eculizumab concentrations

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Figure 10: Simulated and Observed Individual Time Profiles of Eculizumab Concentrations for aHUS Patients in Retrospective (C09-001r) Study with Body Weight 20 to <30 kg

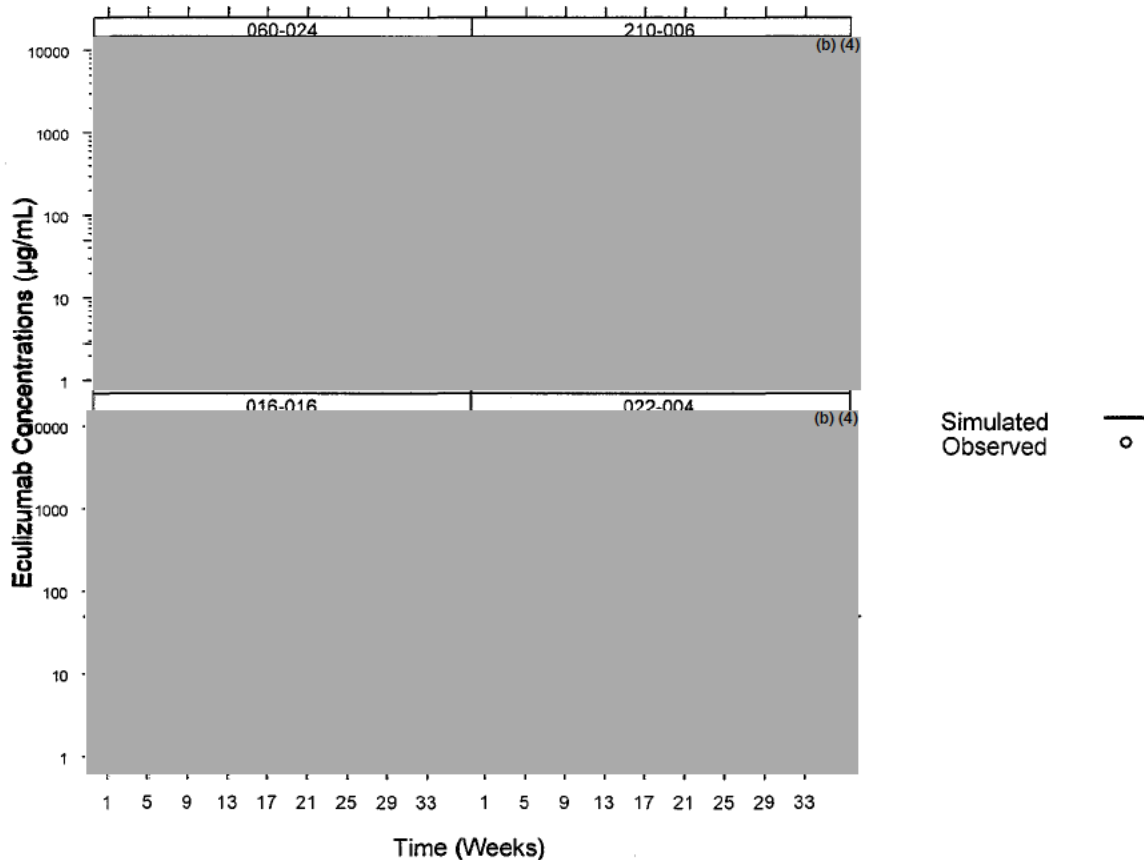


Note: Simulated concentrations were derived with the 600 mg weekly x2 following by 600 mg week 3, 600 mg Q2 weeks

Red lines represent the target window for eculizumab concentrations

**POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS**

**Figure 11: Simulated and Observed Individual Time Profiles of Eculizumab
Concentrations for aHUS Patients in Retrospective (C09-001r) Study with
Body Weight 10 to <20 kg**

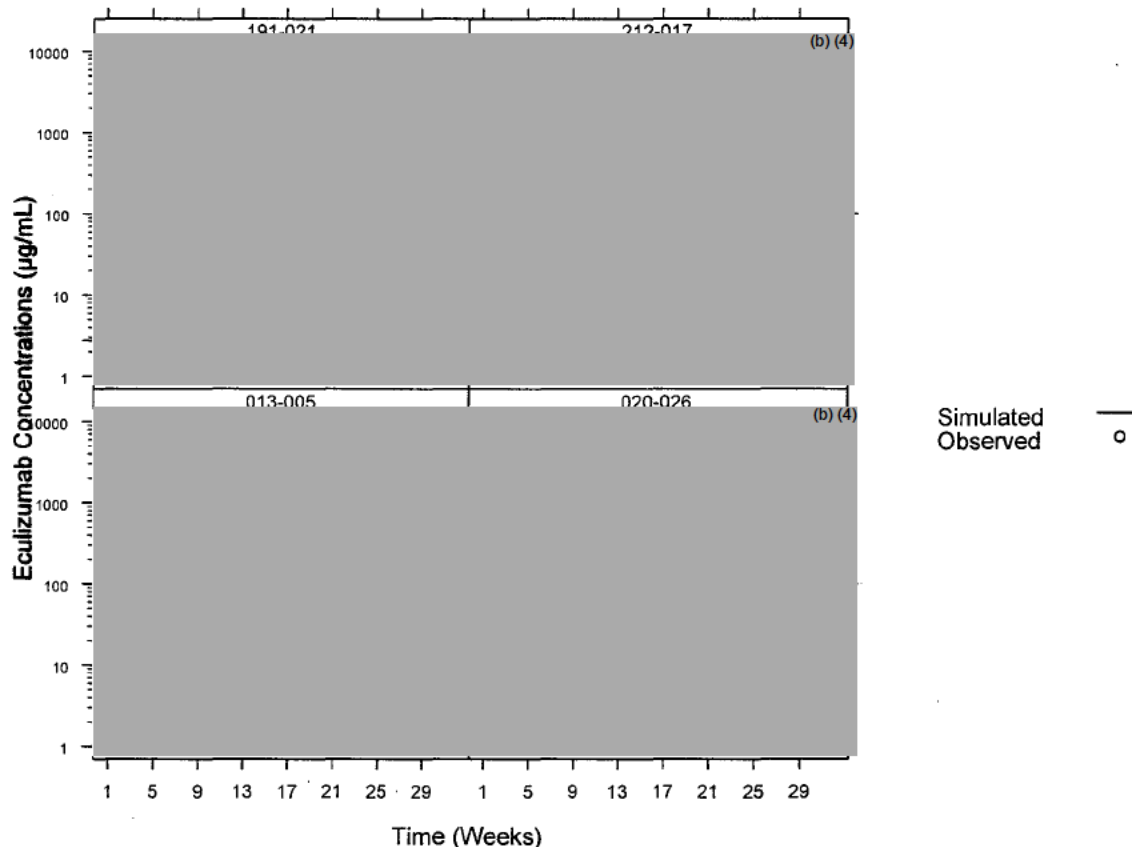


Note: Simulated concentrations were derived with the 600 mg weekly x1 following by 300 mg week 2, 300 mg Q2 weeks

Red lines represent the target window for eculizumab concentrations

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Figure 12: Simulated and Observed Individual Time Profiles of Eculizumab Concentrations for aHUS Patients in Retrospective (C09-001r) Study with Body Weight 5 to <10 kg



Note: Simulated concentrations were derived with the 300 mg weekly x1 following by 300 mg week 2, 300 mg Q2 weeks

Red lines represent the target window for eculizumab concentrations

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
 RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

2.1.5. **Eculizumab – Individual and Descriptive Statistics of PK Parameters of
 Eculizumab**

**Table 5: Eculizumab – Individual and Descriptive Statistics of PK Parameters of
 Eculizumab for Study C08-002A/B**

Patient Identification ^a	CL (L/h)	V _c (L)	T _{1/2} (h)
2-029-001			
2-039-001			
2-040-001			
2-041-001			
2-043-001			
2-045-001			
2-045-002			
2-070-001			
2-110-001			
2-140-001			
2-141-001			
2-191-001			
2-196-001			
2-197-001			
2-198-001			
2-198-002			
2-205-001			
Mean	0.0175	6.40	281
CV (%)	47.5	19.0	28.1
Median			
Minimum			
Maximum			

^a CL=Clearance of eculizumab; CV= Coefficient of variation; T1/2= Elimination half-life; Vc= Volume of central distribution of eculizumab

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
 RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Table 6: Eculizumab – Individual and Descriptive Statistics of PK Parameters of Eculizumab for Study C08-003A/B

Patient Identification ^a	CL (L/h)	V _c (L)	T _{1/2} (h)
3-060-001			
3-060-002			
3-074-001			
3-074-002			
3-079-001			
3-144-001			
3-167-001			
3-196-001			
3-196-002			
3-197-001			
3-197-002			
3-198-001			
3-198-002			
3-198-003			
3-203-001			
3-205-001			
3-243-001			
3-250-001			
3-250-002			
3-250-003			
Mean	0.0121	5.72	337
CV (%)	23.3	17.0	22.1
Median			
Minimum			
Maximum			

^a CL=Clearance of eculizumab; CV= Coefficient of variation; T_{1/2}= Elimination half-life; V_c= Volume of central distribution of eculizumab

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
 RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Table 7: Eculizumab – Individual and Descriptive Statistics of PK Parameters of Eculizumab for Study C09-001r

Patient Identification ^a	CL (L/h)	V _c (L)	T _{1/2} (h)
012-003	(b) (4)		
013-005			
014-009			
016-016			
017-019			
019-025			
020-026			
022-004			
033-001			
044-012			
060-024			
110-007			
120-008			
190-018			
191-021			
210-006			
211-015			
212-017			

**POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
 RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS**

**Table 7: Eculizumab – Individual and Descriptive Statistics of PK Parameters of
 Eculizumab for Study C09-001r (Continued)**

Patient Identification ^a	CL (L/h)	V _c (L)	T _{1/2} (h)
260-011	(b) (4)		
261-013			
Mean	0.0091	3.04	272
CV (%)	77.1	62.6	46.1
Median	(b) (4)		
Minimum			
Maximum			

^a CL=Clearance of eculizumab; CV= Coefficient of variation; T_{1/2}= Elimination half-life; V_c= Volume of central distribution of eculizumab

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
 RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

2.1.6. **Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters of Eculizumab**

Table 8: Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters by Age Group

Population	Protocol (N)	Induction Period			Maintenance Period		
		Parameter ^a	Mean (CV%)	Median (Range)	Parameter	Mean (CV%)	Median (Range)
<2 years of age	C09-001r (N=5)	AUC	36406.41 (26.6)	33929.38 (26297.80 – 51235.28)	AUC	95990.56 (39.5)	90263.57 (61442.67 - 157778.48)
		C _{max}	281.60 (31.4)	276.76 (171.48 - 385.04)	C _{max}	367.46 (12.8)	396.16 (312.60 - 406.49)
		C _{min}	165.99 (32.7)	142.95 (134.60 - 262.84)	C _{min}	121.23 (83.1)	90.37 (17.05 - 235.15)
≥2 – <6 years of age	C09-001r (N=4)	AUC	39537.79 (23.2)	40474.51 (27572.56 – 49629.59)	AUC	56583.21 (29.9)	58939.40 (34429.33 - 74024.72)
		C _{max}	316.37 (29.2)	331.81 (205.51 - 396.35)	C _{max}	278.41 (16.4)	273.32 (228.36 - 338.65)
		C _{min}	171.46 (22.4)	171.47 (129.07 - 213.81)	C _{min}	94.71 (49.4)	105.56 (34.35 - 133.35)

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
 RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

**Table 8: Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters
 by Age Group (Continued)**

Population	Protocol (N)	Induction Period			Maintenance Period		
		Parameter ^a	Mean (CV%)	Median (Range)	Parameter	Mean (CV%)	Median (Range)
≥6 – <12 years of age	C09-001r (N=5)	AUC	31298.91 (14.8)	32072.88 (23723.37 - 36298.63)	AUC	113954.27 (17.5)	111041.20 (93055.00 - 145050.16)
		C _{max}	223.23 (17.3)	225.55 (167.98 - 274.10)	C _{max}	473.70 (9.9)	455.8 (436.00 - 546.04)
		C _{min}	154.34 (13.4)	160.50 (117.80 - 167.32)	C _{min}	233.96 (27.5)	230.52 (162.20 - 334.53)
≥12 - <18 years of age	C08-002A/B (N=1)	AUC	20905.41 (NC)	20905.41 (20905.41 - 20905.41)	AUC	95117.31 (NC)	95117.31 (95117.31 - 95117.31)
		C _{max}	147.43 (NC)	147.43 (147.43 - 147.43)	C _{max}	392.49 (NC)	392.49 (392.49 - 392.49)
		C _{min}	104.29 (NC)	104.29 (104.29 - 104.29)	C _{min}	196.16 (NC)	196.16 (196.16 - 196.16)
	C08-003A/B (N=5)	AUC	22084.74 (14.7)	21208.19 (18586.43 – 26844.60)	AUC	99956.28 (25.2)	109339.41 (62906.27 - 126835.15)
		C _{max}	157.09 (14.0)	152.85 (137.34 - 192.08)	C _{max}	414.74 (19.8)	425.37 (296.33 - 495.87)
		C _{min}	109.22 (16.5)	103.75 (85.38 - 131.73)	C _{min}	205.54 (32.5)	226.55 (108.84 - 279.61)

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
 RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

**Table 8: Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters
 by Age Group (Continued)**

Population	Protocol (N)	Induction Period			Maintenance Period		
		Parameter ^a	Mean (CV%)	Median (Range)	Parameter	Mean (CV%)	Median (Range)
	C09-001r (N=2)	AUC	28908.43 (34.9)	28908.43 (21765.02 - 36051.85)	AUC	95242.06 (18.7)	95242.06 (82667.40 - 107816.71)
		C _{max}	222.03 (39.7)	222.03 (159.73 - 284.33)	C _{max}	457.08 (27.7)	457.07 (367.52 - 546.63)
		C _{min}	130.73 (29.2)	130.73 (103.74 - 157.73)	C _{min}	161.32 (5.7)	161.32 (154.78 - 167.87)
	Pooled (N=8)	AUC	23643.24 (23.7)	21486.60 (18586.43 - 36051.85)	AUC	98172.86 (20.7)	101467.01 (62906.27 - 126835.15)
		C _{max}	172.12 (28.1)	156.29 (137.34 - 284.33)	C _{max}	422.54 (19.3)	408.93 (296.33 - 546.63)
		C _{min}	113.98 (19.7)	104.02 (85.38 - 157.73)	C _{min}	193.31 (28.2)	183.18 (108.84 - 279.61)
≥18 years of age	C08-002A/B (N=16)	AUC	19611.66 (20.7)	19862.87 (12222.98 - 27096.27)	AUC	77693.56 (35.1)	71227.19 (26404.96 - 137647.83)
		C _{max}	145.02 (18.9)	142.00 (100.52 - 195.39)	C _{max}	342.18 (27.0)	329.29 (176.75 - 528.05)
		C _{min}	92.99 (24.4)	92.84 (43.41 - 131.79)	C _{min}	149.03 (46.6)	140.99 (25.90 - 310.43)

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Table 8: Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters by Age Group (Continued)

Population	Protocol (N)	Induction Period			Maintenance Period		
		Parameter ^a	Mean (CV%)	Median (Range)	Parameter	Mean (CV%)	Median (Range)
	C08-003A/B (N=15)	AUC	22928.23 (16.3)	22477.27 (16890.79 – 29401.12)	AUC	104228.22 (17.9)	103869.12 (63204.47 - 132313.05)
		C _{max}	162.92 (18.0)	158.65 (117.03 - 218.64)	C _{max}	431.73 (15.0)	424.86 (287.37 - 529.33)
		C _{min}	113.50 (15.1)	111.73 (81.96 – 138.00)	C _{min}	214.75 (23.8)	209.57 (114.82 - 291.60)
	C09-001r (N=4)	AUC	20537.81 (24.5)	21171.98 (13874.40 – 25932.87)	AUC	63028.85 (32.2)	60061.56 (41881.89 - 90110.39)
		C _{max}	161.79 (23.9)	171.6 (109.06 - 194.9)	C _{max}	316.02 (26.8)	317.23 (211.07 - 418.57)
		C _{min}	90.15 (26.9)	89.71 (60.95 - 120.21)	C _{min}	100.50 (42.4)	88.62 (65.79 - 158.97)
	Pooled (N=35)	AUC	21138.89 (20.0)	21358.24 (12222.98 – 29401.12)	AUC	87389.59 (31.3)	88235.29 (26404.96 - 137647.83)
		C _{max}	154.61 (19.4)	156.69 (100.52 - 218.64)	C _{max}	377.57 (24.3)	391.68 (176.75 - 529.33)
		C _{min}	101.46 (22.3)	101.17 (43.41 – 138.00)	C _{min}	171.65 (41.3)	160.72 (25.90 - 310.43)

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Table 8: Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters by Age Group (Continued)

Population	Protocol (N)	Induction Period			Maintenance Period		
		Parameter ^a	Mean (CV%)	Median (Range)	Parameter	Mean (CV%)	Median (Range)
Overall	Pooled (N=57)	AUC	25012.02 (32.8)	22971.02 (12222.98 - 51235.28)	AUC	89825.89 (31.5)	90110.39 (26404.96 - 157778.48)
		C _{max}	185.58 (37.2)	163.43 (100.52 - 396.35)	C _{max}	384.47 (23.5)	396.16 (176.75 - 546.63)
		C _{min}	118.43 (31.5)	111.73 (43.41 - 262.84)	C _{min}	170.33 (44.0)	167.87 (17.05 - 334.53)

^a AUC= Area under the concentration-time curve from day zero to week one for the induction period and area under the concentration-time curve under steady-state (µg×h/mL), C_{max}= Maximum concentration (µg/mL); C_{min}= Minimum concentration (µg/mL); CV(%)= Coefficient of variation; N= Number of patients; NC= Not calculated

Note: The calculation of PK parameters during the induction period was based on the simulated concentration-time profiles during the first week following the first dose. For the maintenance period, the calculation of PK parameters was based on simulated concentration-time profiles under steady-state conditions.

The dosing regimens used for the simulations were the Alexion Dosing Strategy for pediatric and adolescent patients with aHUS

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Table 9: Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters by Body Weight Group

Population	Protocol	Induction Period			Maintenance Period		
		Parameter ^a	Mean (CV%)	Median (Range)	Parameter	Mean (CV%)	Median (Range)
5 - <10 kg	C09-001r (N=4)	AUC	32699.20 (17.7)	32247.53 (26297.80 – 40003.95)	AUC	94818.72 (46.1)	80026.87 (61442.67 – 157778.48)
		C _{max}	263.91 (34.7)	249.56 (171.48 - 385.04)	C _{max}	360.28 (14.1)	361.03 (312.60 - 406.49)
		C _{min}	141.77 (3.7)	142.66 (134.60 - 147.17)	C _{min}	96.48 (100.8)	66.87 (17.05 - 235.15)
10 - <20 kg	C09-001r (N=4)	AUC	45453.47 (13.1)	45890.77 (38797.06 – 51235.28)	AUC	63246.51 (44.0)	58939.40 (34429.33 – 100677.90)
		C _{max}	353.08 (15.6)	370.30 (275.39 - 396.35)	C _{max}	292.79 (24.7)	273.32 (228.36 - 396.16)
		C _{min}	204.90 (22.8)	202.97 (150.83 - 262.84)	C _{min}	116.42 (68.3)	105.56 (34.35 - 220.20)
20 - <30 kg	C09-001r (N=5)	AUC	32068.74 (9.7)	32072.88 (27572.56 – 36298.63)	AUC	104967.00 (25.0)	101663.90 (74024.72 – 145050.16)
		C _{max}	230.73 (11.7)	225.55 (205.51 - 274.10)	C _{max}	442.50 (16.7)	436.03 (338.65 - 546.04)
		C _{min}	156.60 (10.0)	160.50 (129.07 - 167.32)	C _{min}	212.04 (36.7)	199.57 (133.35 - 334.53)

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

Table 9: Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters by Body Weight Group (Continued)

Population	Protocol	Induction Period			Maintenance Period		
		Parameter	Mean (CV%)	Median (Range)	Parameter	Mean (CV%)	Median (Range)
30 - <40 kg	C09-001r (N=1)	AUC	23723.37 (NC)	23723.37 (23723.37-23723.37)	AUC	11891.07 (NC)	11891.07 (11891.07 - 11891.07)
		C _{max}	167.98 (NC)	167.98 (167.98 - 167.98)	C _{max}	494.64 (NC)	494.64 (494.64 - 494.64)
		C _{min}	117.80 (NC)	117.80 (117.80 - 117.80)	C _{min}	242.98 (NC)	242.98 (242.98 - 242.98)
≥40 kg	C08-002A/B (N=17)	AUC	196987.76 (20.0)	20159.02 (12222.98 – 27096.27)	AUC	78718.49 (34.0)	71899.34 (26404.96 – 137647.83)
		C _{max}	145.16 (18.3)	142.96 (100.52 - 195.39)	C _{max}	345.14 (26.0)	334.63 (176.75 - 528.05)
		C _{min}	93.66 (23.6)	93.50 (43.41 - 131.79)	C _{min}	151.80 (44.9)	141.17 (25.90 - 310.43)
	C08-003A/B (N=20)	AUC	22717.36 (15.6)	22379.16 (16890.79 – 29401.12)	AUC	103160.24 (19.3)	105003.73 (62906.27 – 132313.05)
		C _{max}	161.47 (16.9)	157.67 (117.03 - 218.64)	C _{max}	427.48 (15.8)	425.11 (287.37 - 529.33)
		C _{min}	112.43 (15.1)	111.45 (81.96 – 138.00)	C _{min}	212.45 (25.3)	213.08 (108.84 - 291.60)

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
 RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

**Table 9: Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters
 by Body Weight Group (Continued)**

Population	Protocol	Induction Period			Maintenance Period		
		Parameter	Mean (CV%)	Median (Range)	Parameter	Mean (CV%)	Median (Range)
	C09-001r (N=6)	AUC	23328.02 (31.6)	21881.33 (13874.40 – 36051.85)	AUC	73766.59 (32.8)	73451.90 (41881.89 – 107816.71)
		C _{max}	181.87 (32.1)	172.72 (109.06 – 284.33)	C _{max}	363.04 (31.2)	343.56 (211.07 – 546.63)
		C _{min}	103.68 (31.7)	97.40 (60.95 – 157.73)	C _{min}	120.77 (37.9)	129.92 (65.79 – 167.87)
	Pooled (N=43)	AUC	21604.82 (21.0)	21358.24 (12222.98 – 36051.85)	AUC	89395.78 (29.4)	89179.55 (264004.96 – 137647.83)
		C _{max}	157.87 (21.6)	156.69 (100.52 – 284.33)	C _{max}	385.94 (23.5)	392.49 (176.75 – 546.63)
		C _{min}	103.79 (22.0)	103.75 (43.41 – 157.73)	C _{min}	175.68 (38.7)	170.20 (25.90 – 310.43)

POPULATION PK MODELING – PROSPECTIVE (C08-002A/B AND C08-003A/B) AND
 RETROSPECTIVE (C09-001R) DATA IN AHUS PATIENTS

**Table 9: Eculizumab – Descriptive Statistics of Simulated Exposure PK Parameters
 by Body Weight Group (Continued)**

Population	Protocol	Induction Period			Maintenance Period		
		Parameter	Mean (CV%)	Median (Range)	Parameter	Mean (CV%)	Median (Range)
Overall	Pooled (N=57)	AUC	25012.02 (32.8)	22971.02 (12222.98 - 51235.28)	AUC	89825.89 (31.5)	90110.39 (26404.96 - 157778.48)
		C _{max}	185.58 (37.2)	163.43 (100.52 - 396.35)	C _{max}	384.47 (23.5)	396.16 (176.75 - 546.63)
		C _{min}	118.43 (31.5)	111.73 (43.41 - 262.84)	C _{min}	170.33 (44.0)	167.87 (17.05 - 334.53)

^a AUC= Area under the concentration-time curve from day zero to week one for the induction period and area under the concentration-time curve under steady-state (µg×h/mL), C_{max}= Maximum concentration (µg/mL); C_{min}= Minimum concentration (µg/mL); CV(%)= Coefficient of variation; NC= Not calculated

Note: The calculation of PK parameters during the induction period was based on the simulated concentration-time profiles during the first week following the first dose. For the maintenance period, the calculation of PK parameters was based on simulated concentration-time profiles under steady-state conditions.

The dosing regimens used for the simulations were the Alexion Dosing Strategy for pediatric and adolescent patients with aHUS

11. RESULTS

11.1. Population PK Modeling of Eculizumab

11.1.1. Population PK Analysis of Eculizumab - Protocol C08-002A/B and C08-003A/B

The population PK analysis was performed in a stepwise manner by first modeling the concentrations of eculizumab in serum available from the prospective studies (C08-002A/B and C08-003A/B). A population PK model previously developed in PNH patients (ie, one-compartment model with body weight effect on CL and V_c)⁷ was used to model the concentration-time profiles of eculizumab in the current aHUS population. In addition, the effect of plasma exchange was included in the model.

The PK model was parameterized in terms of clearance (CL) and volume of distribution of the central compartment (V_c). PK parameters were assumed to follow a log-normal distribution and the residual variability in serum concentrations was fitted using a proportional and/or additive error model in the structural model build up. The performance of the PK model to fit serum concentrations of eculizumab is presented in Appendix 1. Individual predicted concentrations of eculizumab were well fitted with the structural population PK model with high and low concentration values well distributed around the line of identity. Overall, the proposed PK model described the eculizumab serum concentrations in aHUS patients with robustness.

Typical values of PK parameters of eculizumab in aHUS patients from prospective studies (C08-002A/B and C08-003A/B) with the final population model are summarized in Table 6.

Table 6: Population PK Analysis of Eculizumab – Protocol C08-002A/B and C08-003A/B

Population PK Parameters ^a	Typical Values	Between Subject Variability (%)
CL (L/h) ^b	$CL = 0.0139 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.764}$	29.6%
V_c (L)	$V_c = 5.95 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.145}$	25.3%
Error Model		
Additive Error (µg/mL)	0, Fix	---
Proportional Error (%)	30.7	---

Note: Correlation between CL and V_c is 45.8%. Shrinkages of CL and V_c are 6.74% and 13.59%, respectively.

^a CL=Clearance of eculizumab; V_c = Volume of central distribution of eculizumab.

^b CL of eculizumab in the prospective study was 3.35 L/h during the plasma exchange (PE) intervention.

Typical CL and V_c values of eculizumab in aHUS patients from prospective studies were 0.0139 L/h and 5.95L, respectively. The elimination half-life ($T_{1/2}$) of eculizumab in aHUS based on the population PK model was 297 hours (corresponding to approximately 12.4 days). These results were consistent with $T_{1/2}$ values of eculizumab previously reported in PNH patients (ie, approximately 10 days).⁷ Between-subjects variabilities (BSV) of CL and V_c in aHUS patients were low and consistent with those previously observed in PNH patients.

The residual variability of the model was low with respect to the ELISA assay. For example, the unexplained error associated to a fitted concentration value of 150 µg/mL would be 46.1 µg/mL (ie, $[150 \mu\text{g/mL} \times 0.307] \mu\text{g/mL}$). This number represents the variability that is not explained by the model and includes the intra-individual variability, the experimental “noise,” and the error arising from the PK modeling itself.

11.1.2. Sources of Variability and Covariate Analysis

Covariate analysis was first performed using graphical methods in order to identify relevant covariates which may affect PK parameters of eculizumab.

Scatter-matrix plots were used to display relationships of continuous covariates and boxplots for relationships of categorical covariates (refer to Appendix 1). The effect of eGFR on PK parameters of eculizumab was evaluated as opposed to chronic kidney disease stages since eGFR is an underlying component for the calculation of chronic kidney disease stages. Moreover, the presence of complement factor mutations did not appear to affect PK parameters of eculizumab. Based on the exploratory figures, the following covariates were selected for the formal covariate analysis in NONMEM (stepwise forward additive and backward elimination approach):

- Clearance (CL): age, sex, time-varying eGFR, patient disease setting group (chronic-PT versus PT-resistant), time-varying hemoglobin and hemoglobin at baseline
- Central volume of distribution (V_c): age, sex, patient disease setting group (chronic-PT versus PT-resistant), time-varying hemoglobin and hemoglobin at baseline

A thorough covariate analysis was performed in NONMEM using a stepwise forward additive (p-value <0.01) and a backward elimination ($P < 0.001$) approach.

None of the covariates tested were included in the model, with the exception of time-varying hemoglobin. On the other hand, the inclusion of this covariate into the population PK model did not reduce the variability of the CL of eculizumab, suggesting that this covariate did not have a clinically relevant impact on the understanding of sources of variability. Sex also was not identified as a statistically significant covariate explaining the CL of eculizumab in aHUS patients.

Overall, the final population PK model of eculizumab in aHUS patients included body weight on CL and V_c , as well as plasma exchange on CL.

11.1.3. Population PK Analysis of Eculizumab - Studies C08-002A/B, C08-003A/B and C09-001r

In a second step, PK data from the retrospective study (C09-001r) was included in the analysis. The performance of the PK model to fit serum concentrations of eculizumab are presented in Appendix 2. Individual predicted concentrations of eculizumab were well fitted with the structural population PK model with high and low concentration values well distributed around the line of identity. Overall, the one-compartment model described the eculizumab serum concentrations with robustness.

In order to evaluate the effect of the retrospective study data on population PK parameters of eculizumab collected in prospective studies, a “study effect” on systemic clearance (CL) and volume of distribution (V_c) of eculizumab was tested and was found to be not significant at the

5% level ($P>0.05$) (refer to Appendix 2). These results suggest that PK parameters of eculizumab in aHUS patients from the prospective and retrospective studies were similar. As a result, data from the prospective and retrospective studies were pooled and a meta analysis was performed on a total 57 aHUS patients. Descriptive statistics of the demographic data in the overall population is provided in Appendix 2.

Typical values of PK parameters of eculizumab from the overall aHUS patient population are summarized in Table 7.

Table 7: Population PK Analysis of Eculizumab – Studies C08-002A/B, C08-003A/B and C09-001r

Population PK Parameters ^a	Prospective Studies ^b (Prospective Population) (N=37)	Prospective and Retrospective Studies ^c (Overall Population) (N=57)
Systemic Parameters		
CL (L/h) ^d	$CL = 0.0139 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.764}$	$CL = 0.0146 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.669}$
V _c (L)	$V_c = 5.95 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.143}$	$V_c = 6.14 \times \left(\frac{\text{Body Weight}}{70} \right)^{0.722}$
Correlation between CL and V _c	45.8%	No correlation on the model
Between Subject Variability		
On CL	29.6%	33.9%
On V _c	25.3%	20.9%
Error Model		
Additive error (µg/mL)	0 Fix	23.0
Proportional error (%)	30.7	31.9

^a CL=Clearance of eculizumab; V_c = Volume of central distribution

^b Protocols C08-002A/B and C08-003A/B

^c Protocols C08-002A/B, C08-003A/B and C09-001r

^d The typical CL of eculizumab in the prospective and the combined studies were 3.35, and 3.66 L/h during the PE intervention, respectively.

Typical CL values of eculizumab in prospective and overall populations were very similar (ie, 0.0139 and 0.0146 L/h, respectively). The power functions of body weight on CL in the prospective and in the overall aHUS populations were consistent (ie, 0.764 and 0.669, respectively). The power function of weight on CL was close to 1, suggesting a linear effect of body weight on CL. The half-life of eculizumab in aHUS patients derived from the CL and V_c was 291 hours (corresponding to approximately 12.1 days).

Finally, the effect of PE intervention on the CL of eculizumab in the prospective and in the overall aHUS populations was 3.35 and 3.66 L/h during the PE intervention, respectively. The half-life of eculizumab in aHUS patients during a PE intervention was approximately 1.26 hours. This finding suggests that a 50% decline in concentrations of eculizumab would be expected following a PE intervention that was approximately 1 hour in duration.

The V_c of eculizumab in the prospective and overall populations was also consistent (ie, 5.95 and 6.14 L, respectively). On the other hand, the power functions of body weight on V_c in the prospective and in the overall populations were 0.143 and 0.722, respectively. The power function of body weight on V_c observed in the overall population (0.722) was more in line with allometry theory (ie, 1) as compared to results derived from prospective population only. These results suggest that the inclusion of the retrospective data in the analysis provided a better characterization of the effect of body weight on V_c , most probably due to the lower range of body weights available in the pediatric population from the retrospective study.

11.2. Simulations to Support the Proposed Dosing Strategies

PK parameters of eculizumab in aHUS patients from prospective studies were fitted using actual dosing recommendations as per protocol (ie, 900 mg weekly for 4 weeks followed by 1200 mg at fifth week, then 1200 mg every other week).

On the other hand, dosing regimens in the retrospective study were determined at the discretion of the treating Physician. Population PK modeling of eculizumab in aHUS patients from the retrospective study was performed by taking into account the actual dosing regimen implemented by the treating physician.

Simulations were performed to assess concentration-time profiles of eculizumab in aHUS patients in the retrospective study assuming they would have received the eculizumab dosing strategy for adults specified in the prospective studies and for pediatric and adolescent patients with aHUS as outlined in Table 5. For cases where aHUS patients received plasmapheresis (PPH) or plasma exchange (PE) in the retrospective study, a supplemental dose similar to the one used in the prospective study was used to simulate concentration-time profiles of eculizumab. Post-hoc PK parameters were used to predict rich concentration-time profiles in all aHUS patients during the induction and maintenance periods to estimate PK exposures (AUC, C_{max} and C_{min}). Descriptive statistics of PK exposure parameters of eculizumab for the prospective and retrospective studies (according to the eculizumab dosing strategy for pediatric and adolescent patients with aHUS and the supplemental dosing scheme) are presented by age group in Table 8 and by weight group in Table 9.

Table 8: Descriptive Statistics of Simulated PK Exposure Parameters by Age Group

Population	Protocol (N)	Parameters ^a	Mean (CV%)	
			Induction Period	Maintenance Period
<2 years of age	C09-001r (N=5)	AUC (µg·h/mL)	36406.41 (26.6)	95990.56 (39.5)
		C_{max} (µg/mL)	281.60 (31.4)	367.46 (12.8)
		C_{min} (µg/mL)	165.99 (32.7)	121.23 (83.1)
≥2 - <6 years of age	C09-001r (N=4)	AUC (µg·h/mL)	39537.79 (23.2)	56583.21 (29.9)
		C_{max} (µg/mL)	316.37 (29.2)	278.41 (16.4)
		C_{min} (µg/mL)	171.46 (22.4)	94.71 (49.4)

Table 8: Descriptive Statistics of PK Exposure Parameters by Age Group (Continued)

Population	Protocol (N)	Parameters ^a	Mean (CV%)	
			Induction Period	Maintenance Period
≥6 - <12 years of age	C09-001r (N=5)	AUC (µg·h/mL)	31298.91 (14.8)	113954.27 (17.5)
		C _{max} (µg/mL)	223.23 (17.3)	473.70 (9.9)
		C _{min} (µg/mL)	154.34 (13.4)	233.96 (27.5)
≥12 - <18 years of age	C08-002A/B (N=1)	AUC (µg·h/mL)	20905.41 (NC)	95117.31 (NC)
		C _{max} (µg/mL)	147.43 (NC)	392.49 (NC)
		C _{min} (µg/mL)	104.29 (NC)	196.16 (NC)
	C08-003A/B (N=5)	AUC (µg·h/mL)	22084.74 (14.7)	99956.28 (25.2)
		C _{max} (µg/mL)	157.09 (14.0)	414.74 (19.8)
		C _{min} (µg/mL)	109.22 (16.5)	205.54 (32.5)
	C09-001r (N=2)	AUC (µg·h/mL)	28908.43 (34.9)	95242.06 (18.7)
		C _{max} (µg/mL)	222.03 (39.7)	457.08 (27.7)
		C _{min} (µg/mL)	130.73 (29.2)	161.32 (5.7)
	Pooled (N=8)	AUC (µg·h/mL)	23643.25 (23.7)	98172.86 (20.7)
		C _{max} (µg/mL)	172.12 (28.1)	422.54 (19.3)
		C _{min} (µg/mL)	113.98 (19.7)	193.31 (28.2)
≥18 years of age	C08-002A/B (N=16)	AUC (µg·h/mL)	19611.66 (20.7)	77693.56 (35.1)
		C _{max} (µg/mL)	145.02 (18.9)	342.18 (27.0)
		C _{min} (µg/mL)	92.99 (24.4)	149.03 (46.6)
	C08-003A/B (N=15)	AUC (µg·h/mL)	22928.23 (16.3)	104228.22 (17.9)
		C _{max} (µg/mL)	162.92 (18.0)	431.73 (15.0)
		C _{min} (µg/mL)	113.50 (15.1)	214.75 (23.8)
	C09-001r (N=4)	AUC (µg·h/mL)	20537.81 (24.5)	63028.85 (32.2)
		C _{max} (µg/mL)	161.79 (23.9)	316.02 (26.8)
		C _{min} (µg/mL)	90.15 (26.9)	100.50 (42.4)
	Pooled (N=35)	AUC (µg·h/mL)	21138.89 (20.0)	87389.59 (31.3)
		C _{max} (µg/mL)	154.61 (19.4)	377.57 (24.3)
		C _{min} (µg/mL)	101.46 (22.3)	171.65 (41.3)

Table 8: Descriptive Statistics of PK Exposure Parameters by Age Group (Continued)

Population	Protocol (N)	Parameters ^a	Mean (CV%)	
			Induction Period	Maintenance Period
Overall	Pooled (N=57)	AUC (µg·h/mL)	25012.02 (32.8)	89825.89 (31.5)
		C _{max} (µg/mL)	185.58 (37.2)	384.47 (23.4)
		C _{min} (µg/mL)	118.43 (31.5)	170.33 (44.0)

Note: The calculation of PK parameters during the induction period was based on the simulated concentration-time profiles during the first week following the first dose. For the maintenance period, the calculation of PK parameters was based on simulated concentration-time profiles under steady-state conditions. Simulations were performed using the eculizumab dosing strategy for pediatric and adolescent patients with aHUS (refer to Table 5).

^a AUC= Area under the concentration-time curve from Day 0 to Week 1 for the induction period and area under the concentration-time curve under steady-state; C_{max}= Maximum concentration; C_{min}= Minimum concentration; CV(%)= Coefficient of variation; N= Number of patients; NC= Not calculated.

Based on the simulations, the proposed dosing regimen resulted in mean C_{min} values of eculizumab above 50 µg/mL during the induction and maintenance periods for all age groups for the prospective and retrospective studies. Furthermore, mean C_{max} values of eculizumab for the prospective and retrospective studies resulted in concentrations less than 700 µg/mL during the induction and maintenance periods for all age groups. Variability of PK parameters during the induction and maintenance periods was low across all age groups. Overall, these results suggest that the proposed dosing regimen resulted in concentrations within the efficacious range (50 to 700 µg/mL) of eculizumab during the induction and maintenance periods for all age groups.

Descriptive statistics of PK parameters during the induction and maintenance periods stratified by body weight range are presented in Table 9.

Table 9: Descriptive Statistics of Simulated PK Exposure Parameters by Body Weight

Body Weight Range	Protocol (N)	Parameters ^a	Mean (CV%)	
			Induction Period	Maintenance Period
5-<10 kg	C09-001r (N=4)	AUC (µg·h/mL)	32699.20 (17.7)	94818.72 (46.1)
		C _{max} (µg/mL)	263.91 (34.7)	360.28 (14.1)
		C _{min} (µg/mL)	141.77 (3.7)	96.48 (100.8)
10-<20 kg	C09-001r (N=4)	AUC (µg·h/mL)	45453.47 (13.1)	63246.51 (44.0)
		C _{max} (µg/mL)	353.08 (15.6)	292.79 (24.7)
		C _{min} (µg/mL)	204.90 (22.8)	116.42 (68.3)
20-<30 kg	C09-001r (N=5)	AUC (µg·h/mL)	32068.74 (9.7)	104967.00 (25.0)
		C _{max} (µg/mL)	230.73 (11.7)	442.50 (16.7)
		C _{min} (µg/mL)	156.60 (10.0)	212.04 (36.7)
30-<40 kg	C09-001r (N=1)	AUC (µg·h/mL)	23723.37 (NC)	11891.07 (NC)
		C _{max} (µg/mL)	167.98 (NC)	494.64 (NC)
		C _{min} (µg/mL)	117.80 (NC)	242.98 (NC)

Table 9: Descriptive Statistics of PK Exposure Parameters by Body Weight (Continued)

Body Weight Range	Protocol (N)	Parameters ^a	Mean (CV%)	
			Induction Period	Maintenance Period
≥40 kg	C08-002A/B (N=17)	AUC (µg·h/mL)	196987.76 (20.0)	78718.49 (34.0)
		C _{max} (µg/mL)	145.16 (18.3)	345.14 (26.0)
		C _{min} (µg/mL)	93.66 (23.6)	151.80 (44.92)
	C08-003A/B (N=20)	AUC (µg·h/mL)	22717.36 (15.6)	103160.24 (19.3)
		C _{max} (µg/mL)	161.47 (16.9)	427.48 (15.8)
		C _{min} (µg/mL)	112.43 (15.1)	212.45 (25.3)
	C09-001r (N=6)	AUC (µg·h/mL)	23328.02 (31.6)	73766.59 (32.8)
		C _{max} (µg/mL)	181.87 (32.1)	363.04 (31.2)
		C _{min} (µg/mL)	103.68 (31.7)	120.77 (37.9)
	Pooled (N=43)	AUC (µg·h/mL)	21604.82 (21.0)	89395.78 (29.4)
		C _{max} (µg/mL)	157.87 (21.6)	385.94 (23.5)
		C _{min} (µg/mL)	103.79 (22.0)	175.68 (38.7)
Overall	Pooled (N=57)	AUC (µg·h/mL)	25012.02 (32.8)	89825.89 (31.5)
		C _{max} (µg/mL)	185.58 (37.2)	384.47 (23.5)
		C _{min} (µg/mL)	118.43 (31.5)	170.33 (44.0)

Note: The calculation of PK parameters during the induction period was based on the simulated concentration-time profiles during the first week following the first dose. For the maintenance period, the calculation of PK parameters was based on simulated concentration-time profiles under steady-state conditions. Simulations were performed using the eculizumab dosing strategy for pediatric and adolescent patients with aHUS (refer to Table 5).

^a AUC= Area under the concentration-time curve from Day 0 to Week 1 for the induction period and area under the concentration-time curve under steady-state; C_{max}= Maximum concentration; C_{min}= Minimum concentration; CV%= Coefficient of variation; N= Number of patients; NC= Not calculated.

The proposed dosing regimen resulted in mean C_{min} values of eculizumab above 50 µg/mL during the induction and maintenance periods for all body weight range in the prospective and retrospective studies. Furthermore, mean C_{max} values of eculizumab for the prospective and retrospective studies resulted in concentrations less than 700 µg/mL during the induction and maintenance periods for all body weight range. Variability of PK parameters during the induction and maintenance periods was low across all body range. Overall, these results further suggest that the proposed dosing regimen resulted in concentrations within the efficacious range of eculizumab for all body weight range during the induction and maintenance periods.

Individual concentration-time profiles of eculizumab in aHUS patients from the retrospective study were also predicted by taking into account the proposed dosing regimen, and also accounting for supplemental doses associated to PT intervention, for cases where a PT intervention was made. For the patient 014-009 receiving PT intervention (ie, PE), an additional dose of eculizumab administered within 60 minutes (300 mg if the dose prior to the intervention was 300 mg and 600 mg if the dose prior to intervention was 600 mg) was included in simulations.

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125166	Brand Name	Soliris
OCP Division (I, II, III, IV, V)	5	Generic Name	Eculizumab
Medical Division	Oncology	Drug Class	Hematology
OCP Reviewer	Bahru A Habtemariam, Pharm.D	Indication(s)	- treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis - treatment of patients with atypical hemolytic uremic syndrome (aHUS).
OCP Team Leader	Julie Bullock, Pharm.D	Dosage Form	Soliris is supplied as 300 mg single-use vials each containing 30 mL of 10 mg/mL sterile, preservative-free eculizumab solution.
Pharmacometrics Reviewer	NA	Dosing Regimen	Varies based on weight. For induction: 300 to 900 mg For maintenance: 300 to 1200 mg
Date of Submission	March 25, 2011	Route of Administration	Soliris should be administered by intravenous infusion over 35 minutes
Estimated Due Date of OCP Review	August 15, 2011	Sponsor	Alexion
Medical Division Due Date	-	Priority Classification	Priority
PDUFA Due Date	September 24, 2011		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	x	2	2	
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	37	37	
Total Number of Studies	1	3	3	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?				
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

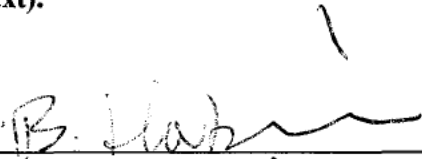
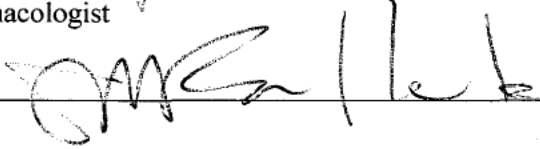
File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
The sponsor will need to submit the following items order to conduct proper review.

1. **Submit datasets used for the population PK and PD modeling in sas transport (*.xpt) format.**
2. **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).**

Bahru A. Habtemariam, Pharm.D.		April 21, 2010
Reviewing Clinical Pharmacologist		Date
Julie Bullock, Pharm.D.		April 21, 2010
Team Leader/Supervisor		Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for
NDA_BLA or Supplement 090808

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125166s172

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

FINAL REMS REVIEW

Date: September 22, 2011

To: Ann Farrell, M.D., Director
Division of Hematology Products (DHP)

Through: Claudia Karwoski, Pharm.D., Director
Division of Risk Management (DRISK) *Claudia B Karwoski*
9/22/11

From: **Scientific Lead**, Risk Management Analyst (RMA) *J Weaver*
Joyce Weaver, Pharm.D., DRISK

Team Leader, Cynthia LaCivita, Pharm.D., DRISK

DRISK Review Team
Kate Heinrich, M.A., Health Communications Analyst
Therese Cvetkovich, M.D., Clinical Reviewer
Sharon Mills, BSN, RN, CCRP, Patient Labeling Reviewer

Subject: Final REMS Review for Soliris (eculizumab)

Drug Name (Established Name): Soliris (eculizumab)

Therapeutic Class: Complement Inhibitor

Dosage and Route: Dose varies by indication, age, and weight;
administered by intravenous infusion

Application Type/Number: BLA 125166

Applicant: Alexion

OSE RCM #: 2011-1313

Tracked Safety Issue: 000611

EXECUTIVE SUMMARY

A proposed Risk Evaluation and Mitigation Strategy (REMS) modification was submitted with a supplement to expand the indication for Soliris (eculizumab) to include the treatment of atypical hemolytic uremic syndrome (aHUS). In addition to incorporating the aHUS indication, the REMS modification includes a narrowing of the focus of the REMS to meningococcal infections; that is, the risks of other serious infections and discontinuation hemolysis were removed from the REMS.

Because the REMS was not performing acceptably in enrolling prescribers, the only element to assure safe use included in the REMS, the modes of prescriber enrollment were expanded to include enrollment via telephone and the internet. The sponsor will be required to submit an interim report, before the next REMS assessment report due June 2012, regarding their progress in enrolling prescribers in the REMS.

1 INTRODUCTION AND BACKGROUND

Soliris was approved for marketing in the United States on March 16, 2007 for the treatment of paroxysmal nocturnal hemoglobinuria to reduce hemolysis. Soliris causes patients receiving the product to be at increased risk for infections, including meningitis, with *Neisseria meningitidis*. A REMS was approved for Soliris June 4, 2010 to mitigate the risks of infection with *Neisseria meningitidis* and to mitigate the outcomes for other serious infections, and the risk of discontinuation hemolysis. The REMS is comprised of a Medication Guide, elements to assure safe use (“Healthcare providers who prescribe Soliris are specially certified and patients are monitored for adverse events”), and a Timetable for Submission of Assessment (every 6 months for 1 year, then annually).

Two REMS assessment reports have been submitted since the REMS was approved. The reports show an unacceptable level of prescriber enrollment in the REMS. The Sponsor was notified that the level of enrollment was not acceptable following the first REMS assessment. However, the latest assessment report, submitted June 1, 2011, reports that only about (b) (4) % of current prescribers are registered in the REMS.

2 MATERIALS REVIEWED

- Proposed REMS modification submitted March 25, 2011
- June 1, 2011 Soliris REMS Assessment covering October 2010-March 2011
- Revised draft REMS and REMS Supporting Document submitted August 26, 2011
- Revised draft REMS and REMS Supporting Document submitted September 19, 2011
- Revised draft REMS and REMS Supporting Document submitted September 22, 2011

3 RESULTS OF REVIEW OF PROPOSED SOLIRIS RISK EVALUATION AND MITIGATION STRATEGY

3.1 Goals

The goals of the REMS are:

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To educate Healthcare Professionals (HCP) and Patients (or Caregivers, or Legal Guardians) 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

3.2 REMS Elements

3.2.1 Medication Guide

The Soliris Medication Guide is an element in the REMS.

3.2.2 Communication Plan

The REMS does not include a communication plan.

3.2.3 Elements to Assure Safe Use

Healthcare providers who prescribe Soliris are specially certified

Prescriber certification is based on prescriber agreement that the prescriber will:

- Counsel patients and provide the patient educational materials to the patient, including the Soliris Patient Safety Card and the Medication Guide
- Provide the Medication Guide to the patient prior to each infusion
- Review the educational materials and the product labeling and comply with the directions for safe use including ensuring patients receive a meningococcal vaccine.
- Promptly report to the Sponsor at 1-888-765-4747 or to the FDA at 1-800-332-1088 cases of meningococcal infection, including the patients' clinical outcomes

3.2.4 Implementation System

The Soliris REMS does not have an implementation system.

3.2.5 Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA every six months for one year, and then annually thereafter from the date of the initial approval of the REMS (6/4/2010).

3.3 REMS Assessment Plan

Information needed for assessments

(b) (4)

- (b) (4)
- The number of patients enrolled in the OneSource Safety Support Program and receiving Soliris treatment (during the reporting period and cumulative)
- The number of patient person-years for enrolled patients on Soliris
- The number of new patients enrolled during the reporting period
- The number of patients who received Soliris who were not enrolled (during the reporting period and cumulative)
- The number of patients who discontinued Soliris (during the reporting period and cumulative)
- The number of patients who were lost to follow up (during the reporting period and cumulative)
- Prescriber enrollment:
 - Numbers enrolled: total and newly enrolled during the reporting period,
 - Number who are prescribing Soliris who are not enrolled
 - Reasons that prescribers did not enroll
 - Actions taken to ensure that all prescribers are enrolled
- An assessment of the following use data for Soliris
 - The number of patients treated by diagnosis
 - The number of pediatric patients

- The percent of patients receiving meningococcal vaccination
- The number and summary of prescribers who were un-enrolled from the OneSource Safety Support Program during the reporting period and cumulative
- Alexion Global Pharmacovigilance will write a narrative summary and analysis of meningococcal infections during the reporting period; this will include for each case:
 - The serotype of *Neisseria meningitides*
 - The type and timing of vaccination and revaccination against *Neisseria meningitides*
 - The circumstances under which the patient sought/received treatment for meningococcal infection, including the patient's use of the Soliris Patient Safety Card
 - The clinical course of the meningococcal infection, and the outcome of the infection
- An assessment of prescriber and patient understanding regarding the safe use of Soliris i.e., the results of surveys administered to prescribers and patients.
- Medication Guide distribution data, including the number of Medication Guides dispensed in comparison to the number of prescriptions shipped during the reporting period, a report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR208.24, a report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- Based on the information submitted, an assessment of and conclusion regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

3.4 Postmarketing Studies

A report on the voluntary patient registry, established when Soliris was approved in 6/2007, is scheduled to be submitted after 5 years (6/2012).

4 DISCUSSION

While reviewing the proposed REMS modification to incorporate the aHUS indication and the most recent REMS assessment report for the Soliris REMS, the review team discussed the usefulness of including the risks of other serious infections and discontinuation hemolysis in the REMS. Experience to date does not show anything remarkable regarding the presentation or management of other serious infections that develop in patients receiving eculizumab. Except for meningococcal

infections, the serious infections that develop in Soliris patients require only the attention and handling that would usually be accorded patients with these infections. Postmarketing experience shows that discontinuation hemolysis is not as likely as was thought when the original application was under consideration. Serious cases of discontinuation hemolysis have not been reported for eculizumab. The review team agreed that the REMS should be focused on meningococcal infection. To this end, the REMS modification includes a narrowing of the focus of the REMS to meningococcal infections; that is, the risks of other serious infections and discontinuation hemolysis were removed from the REMS.

Although the risk of meningococcal infection has been relayed successfully to prescribers and patients (surveys of prescribers and patients show that they are aware of this risk), prescribers have not been enrolled as required by the REMS. Because the REMS was not performing acceptably in enrolling prescribers, the modes of prescriber enrollment were expanded to include enrollment via telephone and the internet. The sponsor was told in a meeting August 22, 2011 that the performance of the program in enrolling (b) (4)% prescribers is unacceptable. We told the sponsor that we would expect all or almost all prescribers to be enrolled. The sponsor will be asked to report on their progress in enrolling prescribers before the next annual REMS assessment report, due June 2012.

5 CONCLUSION

All issues related to the REMS modification have been resolved. The REMS should be approved.

6 RECOMMENDATIONS

The REMS should be approved.

The information in **Information needed for assessments**, section 3.3, above, should be included in the approval letter. The approval letter should also include the requirement for an interim report on the progress in enrolling prescribers in the REMS as of 120 days following approval of the REMS modification. This report should be submitted by March 1, 2012.

ATTACHMENTS (REMS document and all appended materials.)

Initial REMS Approval: 6/4/2010
Most Recent Modification: 9/22/2011

BLA 125166 Soliris® (eculizumab)
Recombinant Humanized Monoclonal Antibody

Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410

(203) 272-2596

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S)

The goals of the REMS are:

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

II. REMS ELEMENTS

A. Medication Guide

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

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

B. Elements to Assure Safe Use

Healthcare providers who prescribe Soliris are specially certified.

- a. Prescriber certification is based on prescriber agreement that the prescriber will:
 - i) Counsel patients and provide the patient educational materials to the patient, including the Soliris Patient Safety Card and the Medication Guide
 - ii) Provide the Medication Guide to the patient prior to each infusion
 - iii) Review the educational materials (Soliris Patient Safety Card, Prescriber Introductory Letter, Prescriber Safety Brochure, *Important Safety Information about Soliris*, Patient Safety Brochure, *Important Safety Information about Soliris*, and Dosing and Administration Guide) and the product labeling and comply with the directions for safe use including ensuring patients receive a meningococcal vaccine.
 - iv) Promptly report to the Sponsor at 1-888-765-4747 or to the FDA at 1-800-332-1088 cases of meningococcal infection, including the patients' clinical outcomes
- b. The prescriber will fax the completed enrollment form to 1-877-580-2596 (ALXN), email the completed form to OSSP@alxn.com, or mail the form to Alexion at Alexion Pharmaceuticals, 352 Knotter Drive, Cheshire, CT 06410, Attn: OneSource Safety Support Program.

A prescriber may also complete the enrollment by phone with Alexion at 1-888-765-4747 or electronically via the Soliris REMS website at www.soliris.net
- c. Alexion will contact certified prescribers annually and provide the educational materials (Medication Guide, Soliris Patient Safety Card, Prescriber Safety Brochure, *Important Safety Information about Soliris*, Patient Safety Brochure, *Important Safety Information about Soliris*, and Dosing and Administration Guide). The educational materials and enrollment form will be available on a REMS-dedicated webpage accessible from www.soliris.net.
- d. The following materials are part of the REMS and are appended
 - (1) Soliris Patient Safety Card
 - (2) Prescriber Introductory Letter and Enrollment Form
 - (3) Patient Safety Brochure, *Important Safety Information about Soliris*
 - (4) Prescriber Safety Brochure, *Important Safety Information about Soliris*
 - (5) Dosing and Administration Guide

(6) REMS website

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

C. Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA every six months for one year, and then annually thereafter from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Alexion will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDICES

The following documents are appended:

- (1) Soliris Patient Safety Card
- (2) Prescriber Introductory Letter and Enrollment Form
- (3) Patient Safety Brochure, *Important Safety Information about Soliris*
- (4) Prescriber Safety Brochure, *Important Safety Information about Soliris*
- (5) Dosing and Administration Guide
- (6) REMS website (screenshots)

Appendix 1
Soliris Patient Safety Card

PATIENT SAFETY INFORMATION CARD



Important Safety Information for Patients Taking Soliris®

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

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever of 103°F (39.4°C) or higher
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light



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

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

PATIENT SAFETY INFORMATION CARD

+ Information for the Treating Physician



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

- Meningococcal infections may 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).

+ 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®
(e c u l i z u m a b)

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Appendix 2
Prescriber Introductory Letter and Enrollment Form

Dear Soliris® (eculizumab) Prescriber.

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

To get started in the Program, please complete the Prescriber Enrollment Form on the reverse side and either drop it in the mail; fax it to the Soliris OneSource Safety Support Program at 1.877.580.2596 (ALXN); or scan and e-mail it to OSSP@alxn.com.

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

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

I agree to:

- Review the product labeling and educational materials, and comply with the safety instructions for use, including ensuring meningococcal vaccination status
- Counsel patients (or caregivers, or legal guardians) and provide educational materials to the patient (or caregivers, or legal guardians), including the Soliris Patient Safety Information Card, and the Soliris Medication Guide
- Intend to promptly report cases of meningococcal infection, including the patient's clinical outcomes, by contacting the OneSource Safety Support Program (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 www.fda.gov/medwatch
- Revaccinate patients in accordance with the Advisory Committee on Immunization Practices (ACIP) recommendations for the duration of Soliris therapy

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected

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

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

INDICATIONS AND USAGE

Soliris is a complement inhibitor indicated for:

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

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

CONTRAINDICATIONS

Soliris is contraindicated in:

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

The most frequently reported adverse reactions in aHUS single arm prospective trials ($\geq 15\%$ combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

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

Name (printed): _____

Signature: _____ Date: _____

Title: _____

Office Address: _____ E-mail: _____

City: _____ State: _____ ZIP: _____ Country: _____

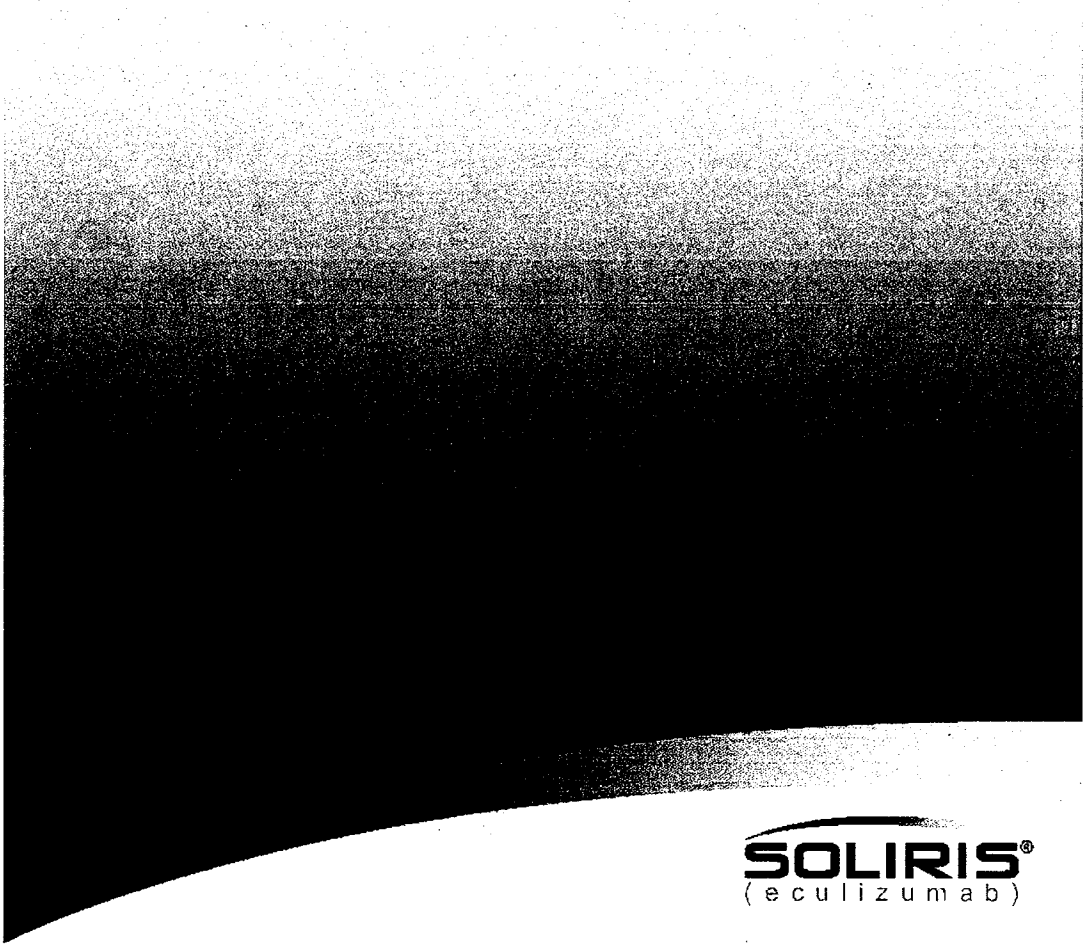
Phone Number: _____ Fax Number: _____

Appendix 3

Patient Safety Brochure, *Important Safety Information about Soliris*

Before starting on Soliris®.

Important safety information for patients



SOLIRIS®
(eculizumab)



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

- Medication Guide
- Soliris Patient Safety Information Card

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



Patient Safety Information Card

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

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

PATIENT SAFETY INFORMATION CARD



**Important Safety Information for
Patients Taking Soliris®**

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

Soliris OneSource™ Treatment Support Program

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

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

SOLIRIS®
(eculizumab)

3



For Discussion With Patients— Important Safety Information

MEDICATION GUIDE

Soliris® (so-leer-is) (eculizumab)

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

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

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

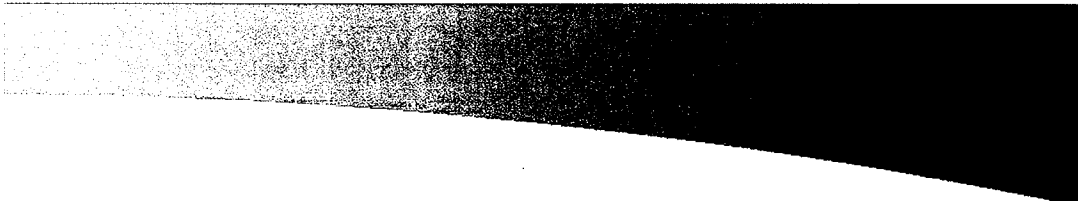
- **Soliris increases your risk of getting serious and life-threatening meningococcal infections**

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

1. **You must receive a meningococcal vaccine at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decides that urgent treatment with Soliris is needed, you should receive a meningococcal vaccine as soon as possible.**
2. **If you had a meningococcal vaccine in the past, you might need a booster dose before starting Soliris. Your doctor will decide if you need another dose of a meningococcal vaccine.**
3. **A meningococcal vaccine does not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:**

— headache with nausea or vomiting	— fever and a rash
— headache and a fever	— confusion
— headache with a stiff neck or stiff back	— muscle aches with flu-like symptoms
— fever of 103°F (39.4°C) or higher	— eyes sensitive to light

Please see back cover for Important Safety Information.
Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.



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

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

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

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

What is Soliris?

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

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). PNH affects red blood cells.
- a disease called atypical Hemolytic Uremic Syndrome (aHUS). aHUS affects the blood system, kidney, and sometimes other body organs.

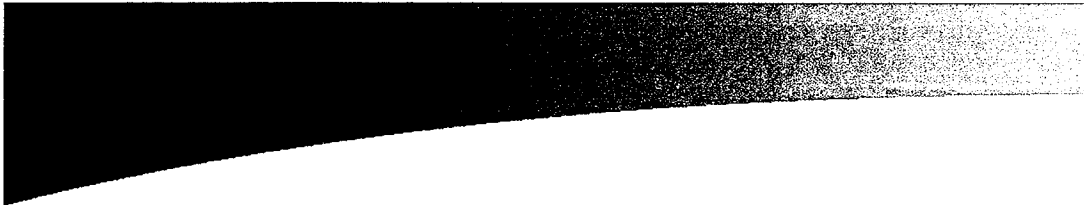
Soliris works by blocking part of your immune system. This can help your symptoms but it can also increase your chance for infection.

It is important that you:

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

SOLIRIS[®]
(eculizumab)

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For Discussion With Patients— Important Safety Information (continued)

Who should not receive Soliris®?

Do not receive Soliris if you:

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

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if you:

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

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

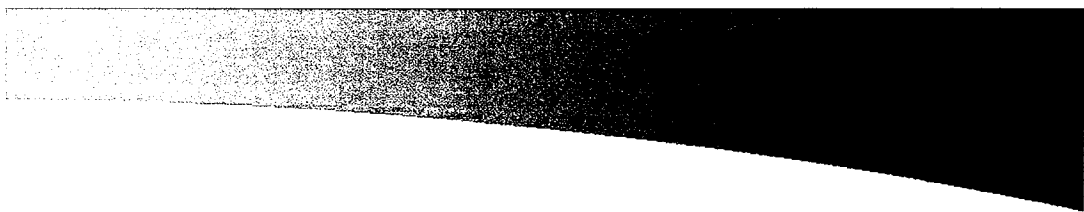
Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes. If you have an allergic reaction during your Soliris infusion, your doctor may decide to give Soliris more slowly or stop your infusion.
- If you are an adult, you will usually receive a Soliris infusion by your doctor:
 - weekly for five weeks, then
 - every 2 weeks
- If you are less than 18 years of age, your doctor will decide how often you will receive Soliris depending on your age and body weight.
- After each infusion, you should be monitored for one hour for allergic reactions. See “What are the possible side effects of Soliris?”
- If you forget or miss a Soliris infusion, call your doctor right away.

Please see back cover for Important Safety Information.

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



- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris®. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**

Symptoms or problems that can happen due to red blood cell breakdown include:

- drop in the number of your red blood cells
- drop in your platelet count
- confusion
- chest pain
- kidney problems
- blood clots
- difficulty breathing

- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

Symptoms or problems that can happen with abnormal clotting may include:

- stroke
- confusion
- seizures
- chest pain (angina)
- difficulty breathing
- kidney problems
- swelling in arms or legs
- a drop in your platelet count

What are the possible side effects of Soliris?

Soliris can cause serious side effects, including:

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

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

SOLIRIS®
(eculizumab)

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For Discussion With Patients— Important Safety Information (continued)

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

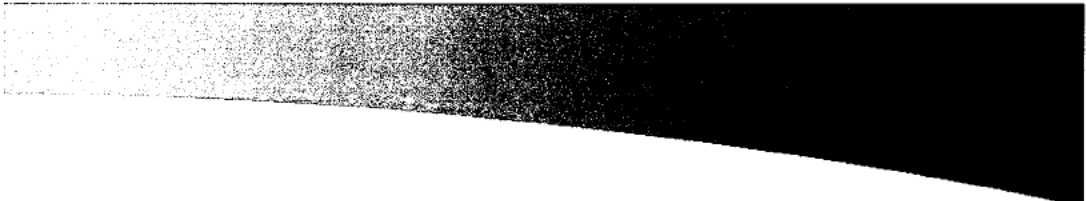
- headaches
- runny nose and colds
- sore throat
- back pain
- nausea

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

- high blood pressure
- common cold (upper respiratory infection)
- diarrhea
- headache
- nausea and vomiting
- low red blood cell count
- low white blood cell count
- urinary tract infection

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 Soliris®

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

What are the ingredients in Soliris?

Active ingredient: eculizumab

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

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

Manufactured by Alexion Pharmaceuticals, Inc.
352 Knotter Drive, Cheshire, CT 06410 USA.

Revised: 09/2011

SOLIRIS®
(eculizumab)

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Want to learn more about Soliris®?

- Visit www.Soliris.net
- Call 1.888.SOLIRIS (1.888.765.4747)

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected

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

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

The most frequently reported adverse reactions in aHUS single arm prospective trials ($\geq 15\%$ combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

ALEXION

SOLIRIS®
(eculizumab)

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Appendix 4

Prescriber Safety Brochure, *Important Safety Information about Soliris*

Before starting your patients on Soliris®.

Important safety information for the healthcare provider

SOLIRIS[®]
(e c u l i z u m a b)



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

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

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

Patient Safety Information Card

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

Prescribers should advise patients to seek medical attention immediately if they develop headache with nausea or vomiting, or headache and fever, even if they don't have their Patient Safety Information Card with them.

PATIENT SAFETY INFORMATION CARD



Important Safety Information for Patients Taking Soliris®

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

SOLIRIS[®]
(eculizumab)

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For Discussion With Patients— Important Safety Information

MEDICATION GUIDE

Soliris® (so-leer-is) (eculizumab)

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

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

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

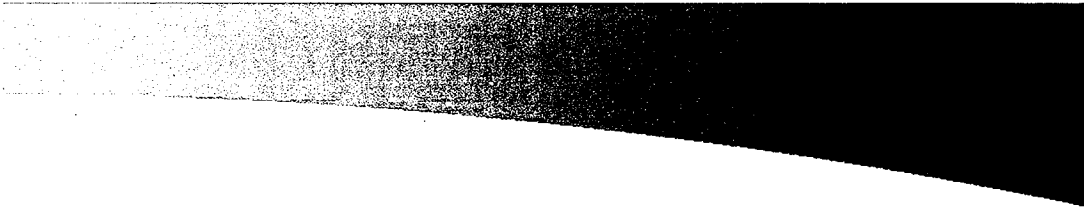
- Soliris increases your risk of getting serious and life-threatening meningococcal infections.

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

1. You must receive a meningococcal vaccine at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decides that urgent treatment with Soliris is needed, you should receive a meningococcal vaccine as soon as possible.
2. If you had a meningococcal vaccine in the past, you might need a booster dose before starting Soliris. Your doctor will decide if you need another dose of a meningococcal vaccine.
3. A meningococcal vaccine does not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:

— headache with nausea or vomiting	— fever and a rash
— headache and a fever	— confusion
— headache with a stiff neck or stiff back	— muscle aches with flu-like symptoms
— fever of 103°F (39.4°C) or higher	— eyes sensitive to light

Please see back cover for Important Safety Information.
Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.



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

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

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

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

What is Soliris?

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

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). PNH affects red blood cells.
- a disease called atypical Hemolytic Uremic Syndrome (aHUS). aHUS affects the blood system, kidney, and sometimes other body organs.

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

It is important that you:

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

SOLIRIS[®]
(e c u l i z u m a b)

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For Discussion With Patients— Important Safety Information (continued)

Who should not receive Soliris®?

Do not receive Soliris if you:

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

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if you:

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

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

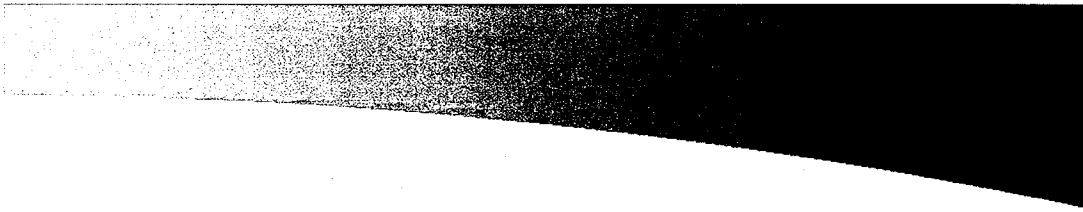
Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes. 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?”

Please see back cover for Important Safety Information.

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



- If you forget or miss a Soliris® infusion, call your doctor right away.
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**

Symptoms or problems that can happen due to red blood cell breakdown include:

- drop in the number of your red blood cells
- drop in your platelet count
- confusion
- chest pain
- kidney problems
- blood clots
- difficulty breathing

- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

Symptoms or problems that can happen with abnormal clotting may include:

- stroke
- confusion
- seizures
- chest pain (angina)
- difficulty breathing
- kidney problems
- swelling in arms or legs
- a drop in your platelet count

What are the possible side effects of Soliris?

Soliris can cause serious side effects, including:

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

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

SOLIRIS[®]
(e c u l i z u m a b)

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For Discussion With Patients— Important Safety Information (continued)

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

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

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

- high blood pressure
- common cold (upper respiratory infection)
- diarrhea
- headache
- nausea and vomiting
- low red blood cell count
- low white blood cell count
- urinary tract infection

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 Soliris®

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

What are the ingredients in Soliris?

Active ingredient: eculizumab

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

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

Manufactured by Alexion Pharmaceuticals, Inc.
352 Knotter Drive, Cheshire, CT 06410 USA.

Revised: 09/2011

SOLIRIS®
(eculizumab)

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Want to learn more about Soliris®?

- Visit www.Soliris.net
- Call 1.888.SOLIRIS (1.888.765.4747)

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected

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

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

The most frequently reported adverse reactions in aHUS single arm prospective trials ($\geq 15\%$ combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

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(eculizumab)

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Appendix 5
Dosing and Administration Guide

SOLIRIS[®]
(eculizumab)

PNH | aHUS

For Paroxysmal Nocturnal Hemoglobinuria (PNH) and atypical Hemolytic Uremic Syndrome (aHUS) patients

Dosing and Administration

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.

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

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

ONESOURCE[™]
TREATMENT SUPPORT

IMPORTANT SAFETY INFORMATION

IMMUNE, SERIOUS, AND/NEUROLOGICAL INFECTIONS

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

- Concomitantly with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with a meningococcal vaccine 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 Soliris Meningococcal Infections for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infection, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program. Enrollment in the Soliris REMS program and additional information are available by telephone, 1-866-SOLIRIS (1-866-765-4747).

Indications and usage

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

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

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris to patients with aHUS.

LIMITATION OF USE

Soliris is not indicated for the treatment of patients with Stage 1 or 2 complement hemolytic uremic syndrome (CHUS).

Adverse reactions

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

The most frequently reported adverse reactions in aHUS single arm prospective trial (≥15% combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

Prescribers enclosed All Prescribing Information for Soliris, including boxed WARNING regarding serious meningococcal infection.

For patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Soliris® (eculizumab) PNH Dosing Guide

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

Soliris is a chronic therapy for a chronic disease!

Patient Category	Induction Phase				Maintenance Phase
	1	2	3	4	
all symptomatic PNH patients	600 mg	600 mg	600 mg	600 mg	600 mg
asymptomatic patients	600 mg	600 mg	600 mg	600 mg	600 mg

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

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

- First dose on time is critical to control chronic, complement-mediated hemolysis; for breakthrough hemolysis, dosing may be adjusted to every 12 days instead of 14 days!
- The dosing adjustments recommended based on age, gender, race, or renal insufficiency!
- Pre-medications are not routinely required.

Monitoring After Discontinuation

Monitor patients after discontinuing Soliris for at least 6 weeks to detect hemolysis.

Important Administration Information

Soliris must be diluted to a final solute concentration of 5 mg/mL prior to administration.

The diluted soliris is a clear, colorless Solis and should be prediluted free of any particles.

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

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

→ To learn more about Soliris, please call 1-866-SOLIRIS (1-866-765-4747) or visit www.Soliris.com.

SOLIRIS
(eculizumab)

For patients with atypical Hemolytic Uremic Syndrome (aHUS)

Soliris® (eculizumab) aHUS Dosing Guide

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

Soliris is a therapy for aHUS—a chronic disease needing chronic treatment¹

Post-treatment	Induction Phase	Maintenance Phase
23 weeks	3	4
Before PEXIDEA	3	4
Afterward (including Soliris)	3	4

Body Weight	Induction Phase	Maintenance Phase
42 kg and over	900 mg weekly for 4 doses	900 mg every 2 weeks for 2 weeks, then 1200 mg every 2 weeks
30 kg to less than 42 kg	600 mg weekly for 4 doses	600 mg every 2 weeks for 2 weeks, then 800 mg every 2 weeks
22 kg to less than 30 kg	300 mg weekly for 4 doses	300 mg every 2 weeks for 2 weeks, then 400 mg every 2 weeks
14 kg to less than 22 kg	300 mg weekly for 4 doses	300 mg every 2 weeks for 2 weeks, then 400 mg every 2 weeks

→ Soliris should be administered at the recommended dosing interval or within 2 days before or after these time points.



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

Supplemental dosing of Soliris is required for patients undergoing concomitant plasma therapy¹

Type of Intervention	Max. Recommended Soliris Dose	Supplemental Soliris Dose With Each PEXIDE Intervention	Timing of Supplemental Soliris Dose
Plasmapheresis or plasma exchange	900 mg	900 mg per 100L of plasma exchanged or plasma exchange volume	Within 48 hours after each plasmapheresis or plasma exchange
Fresh frozen plasma infusion	900 mg or more	900 mg per each 4 L of fresh frozen plasma	60 minutes after each 4 L unit of fresh frozen plasma infusion

PEXIDE = plasmapheresis or plasma exchange, or fresh frozen plasma infusion

Monitoring After Discontinuation

Thrombotic thrombocytopenic syndrome (TMA) complications after discontinuation were observed in the aHUS clinical studies.¹

aHUS patients who discontinue treatment with Soliris should be monitored closely for at least 12 weeks for signs and symptoms of TMA complications. If TMA complications occur after Soliris discontinuation, consider reinitiation of Soliris treatment, plasma therapy¹ or appropriate organ-specific supportive measures.¹

DO NOT ADMINISTER AS AN IV PUSH OR SOLUS INJECTION.

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

→ To learn more about Soliris, please call 1.888.SOLIRIS (1.888.766.4747) or visit www.Soliris.net.

PEXIDE Therapy = plasmapheresis, plasma exchange, or fresh frozen plasma infusion (FFPI).

SOLIRIS
(eculizumab)

For PMH and aHUS

Preparation of Soliris® (eculizumab) for Administration¹

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

Soliris Dose	Diluent Volume	Final Volume
300 mg	30 mL	60 mL
400 mg	40 mL	80 mL
600 mg	60 mL	120 mL
1200 mg	120 mL	240 mL

1. Withdraw the required amount of Soliris from the vial into a sterile syringe and transfer the recommended dose to an infusion bag.
2. Dilute Soliris to a final concentration of 5 mg/mL using the above table as a guideline. The volume of diluent should be equivalent to the drug volume.
3. Carefully invert the infusion bag containing the diluted solution to ensure thorough mixture of the product and the diluent.
 - Discard any wasted portion left in the vial, as the product contains no preservatives.
4. Inspect visually for particulate matter and discoloration prior to administration.
 - The diluted solution is a clear, colorless liquid and should be practically free of any particles.
5. Allow the solution to adjust to room temperature prior to administration (18°C-25°C, 64°F-77°F). It must not be heated in a microwave or with any heat source other than ambient air temperature.
6. A diluted solution of Soliris is stable for 24 hours at 2°C-8°C (36°F-44°F) and at room temperature.

Please see enclosed Full Prescribing Information for Soliris, including **Black Box Warning** regarding serious meningococcal infection.

How Supplied/Storage and Distribution¹

- Vial—30 mL, liquid
- Product strength—10 mg/mL
- Product count—300 mg/30 mL (vial)
- Product physical specs—1 vial per carton
 - Shipped just in time for infusion
 - Weight: <1 lb
 - Dimensions: 1.425" x 1.425" x 3.125"
- Must be stored in the original carton until time of use under conditions at 2°C-8°C (36°F-46°F)
- Protect from light
- Do NOT FREEZE; DO NOT SHAKE
- Do not reuse beyond the expiration date stamped on the carton
- NDC 25682-001-01: Each single-unit carton contains one 30 mL vial of Soliris (10 mg/mL)



→ To enroll in the Soliris REMS and order Soliris, please call 1.888.SOLIRIS (1.888.765.4747)

Diagnosis code: XXXXXX
I code: J1300
Procedure code: XXXXXX



Contact Soliris OneSource at 1.888.SOLIRIS (1.888.765.4747)

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



WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

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

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

References: 1. Soliris® (package insert). Chesler, CE: Alexion Pharmaceuticals, Inc; 2011. 2. Helley D, de Latour RP, Pouches R, et al. French Society of Hematology. Evaluation of hemostasis and endothelial function in patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab. *Blood* 2010; 115:124-131.

ALEXION
Soliris® is a registered trademark of Alexion Pharmaceuticals, Inc.
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Appendix 6
REMS website (screenshots)

Soliris REMS Information - Windows Internet Explorer
http://solirisrems-staging/index.html

ONESOURCE™
SAFETY SUPPORT

Home | [Prescribing Information](#) | [Medication Guide](#) | [Important Safety Information](#)

Increased Risk of Meningococcal Infection and Soliris: Risk Evaluation and Mitigation Strategy (REMS)

Prescribers must enroll in the Soliris REMS to prescribe Soliris.

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

The goals of the Soliris REMS, the OneSource Safety Support Program, are:

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To inform and educate Healthcare Professionals (HCP) and Patients (or Caregivers, or Legal Guardians) 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.

Physicians prescribing Soliris must enroll in the REMS.

To enroll in the program, download and complete the Prescriber Introductory Letter and Enrollment Form and either drop it in the mail, fax it to Soliris OneSource Safety Support Program at 1-877-580-2596 (ALXN); or scan and e-mail it to OSSP@alxn.com

- [Prescriber Introductory Letter and Enrollment Form](#)
- [Patient Introductory Letter and Voluntary Enrollment Form](#)
- [Dosing and Administration Guide](#)
- [Soliris Patient Safety Card](#)
- [Prescriber Brochure, Important Safety Information about Soliris](#)
- [Patient Safety Brochure, Important Safety Information about Soliris](#)

The Soliris Patient Safety Card

Provide your patient with a Soliris Patient Safety Card to carry with them at all times. This safety card contains important safety information about the risk of meningococcal infection that your patient needs to be aware of before they are given Soliris and during their treatment with Soliris. Remind them to show this card to any doctor involved in their treatment.

Tell your patients that if they cannot reach their doctor, go to an emergency room immediately and show emergency room staff the Soliris Patient Safety Card. *Even if they stop using Soliris*, patients should keep their Soliris Patient Safety Card with them for 3 months after the last Soliris dose, since side effects may occur a long time after their last dose of Soliris.

To order a Soliris Patient Safety Information Card, contact OneSource™ at 1.888.SOLIRIS® (1.888.765.4747®).





Home > Product Information > Medication Guide > Important Safety Information

Important Safety Information

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning.

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with a meningococcal vaccine 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 Serious Meningococcal Infections for additional guidance on the management of the risk of meningococcal infections.)
- Monitor patients for early signs of meningococcal infection, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program. Enrollment in the Soliris REMS program and additional information are available by telephone: 1 888 SOLIRIS-9 (1 888-765-4747-9).

INDICATIONS AND USAGE

Paroxysmal Nocturnal Hemoglobinuria (PNH)

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

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.

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

CONTRAINDICATIONS

Soliris is contraindicated in:

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

WARNINGS AND PRECAUTIONS

Other Infections

Soliris blocks terminal complement activation, therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. 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.

Monitoring 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 studies, 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, anuria, 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 reinitiation of Soliris treatment, plasma therapy (plasmapheresis, plasma exchange, or fresh frozen plasma infusion [FFPI]), or appropriate organ-specific supportive measures.

Thrombotic 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.

Laboratory Monitoring

PNH

Serial LDH levels increase during hemolysis and may assist in monitoring Soliris effects, including the response to discontinuation of therapy. In clinical studies, six patients achieved a reduction in serum LDH levels only after a decrease in the Soliris dosing interval from 14 to 12 days. All other patients achieved a reduction in serum LDH levels with the 14-day dosing interval [see Clinical Pharmacology and Clinical Studies].

aHUS

Early signs of thrombotic microangiopathy (TMA) include a decrease in platelet count, and increases in serum LDH and creatinine levels. Follow patients for signs of TMA by monitoring serial platelet counts, serum LDH, and creatinine during Soliris therapy and following discontinuation of Soliris.

Infection Reactions

As with all protein products, 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 initiate appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

ADVERSE REACTIONS

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

The most frequently reported adverse reactions in aHUS single-arm prospective trials (≥15% combined per patient incidence) are: hypotension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

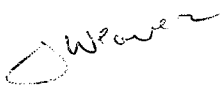
DRISK INTERIM REMS REVIEW

REMS Comments Set #2

Date: September 2, 2011

To: Ann Farrell, M.D., Director
Division of Hematology Products (DHP)

Through: Claudia Karwoski, Pharm.D., Director
Division of Risk Management (DRISK)

From: **Scientific Lead**, Risk Management Analyst (RMA) 
Joyce Weaver, Pharm.D., DRISK

Team Leader, Cynthia LaCivita, Pharm.D., DRISK 

DRISK Review Team

Kate Heinrich, M.A., Health Communications Analyst
Therese Cvetkovich, M.D., Clinical Reviewer

Subject: Interim REMS Review Comments Set 2 for Soliris
(eculizumab)

Drug Name (Established Name): Soliris (eculizumab)

Therapeutic Class: Complement Inhibitor

Dosage and Route: Dose varies by indication, age, and weight;
administered by intravenous infusion

Application Type/Number: BLA 125166

Applicant: Alexion

OSE RCM #: 2011-1313

Tracked Safety Issue: 000611

1 Materials Reviewed

- Revised draft REMS and REMS Supporting Document submitted August 26, 2011

2 Introduction and Background

FDA comments on the REMS were sent to the Alexion August 19, 2011. The FDA edits were discussed with Alexion in a teleconference August 22, 2011. On August 26, 2011, Alexion submitted a revised REMS proposal incorporating FDA edits and language agreed upon during the teleconference.

3 Status of Proposed REMS

The following points were agreed upon in the August 22 teleconference:

- The focus of the REMS should be narrowed to the risk of meningococcal infection.
- Some of the language in the REMS and REMS Supporting Document cannot be decided until labeling has been negotiated.
- It is appropriate for the REMS to include language referencing caregivers and legal guardians of patients, in addition to patients.
- Additional approaches need to be implemented to enroll prescribers, including enrolling via telephone, and enrolling via the internet.
- An additional interim report, before the next scheduled REMS assessment report, to update the FDA on the progress in enrolling prescribers in the REMS, an element that was not satisfactory in the first two REMS assessment reports. The 60-day data cut-off for the next annual REMS assessment report makes an interim 6-month report impractical to show progress in enrolling prescribers following approval of the REMS modification.

In addition to responding to FDA comments on the REMS and REMS Supporting Document, the sponsor developed and submitted a new Soliris Patient Safety Card. The new card was developed based on user feedback that the Soliris Patient Safety Card currently in use does not attract sufficient attention in emergency room settings when presented to emergency room staff. The new Soliris Patient Safety Card was tested with emergency room staff (n=25) against the current Soliris Patient Safety Card, the Nplate Patient Safety Card, and another (b) (4). The new Soliris Patient Safety Card was judged by emergency room staff as better than the other cards tested in capturing the attention of the reader, clearly communicating its message, and creating a sense of urgency among the staff tested. (b) (4). The new Soliris Patient Safety Card was submitted with the modified REMS proposal.

As an additional effort to facilitate prescriber enrollment, the sponsor proposes to combine the Prescriber Introductory Letter and the Prescriber Enrollment Form in a business reply card format that can easily be mailed back to Alexion in a self-addressed postage paid envelope.

4 Discussion

Most of the issues with the REMS have been resolved based on the FDA edits sent to the sponsor, and the discussion held with the sponsor August 22. An issue that has not been raised with the sponsor is that the REMS materials, including the e-capable prescriber enrollment form, should be housed within a REMS-dedicated webpage that can be reached from www.Soliris.net. The REMS-dedicated webpage should be a final destination; that is, once in the REMS-dedicated webpage, the user should be able to access only REMS materials, and should not be able to access marketing materials. Screen shots of the REMS web landing page should be submitted, and the screen shots should be appended to the REMS.

The changes to the Soliris Patient Safety Card and the consolidation of the Prescriber Introductory Letter and the Prescriber Enrollment Form are acceptable.

Regarding the extra assessment proposed at the teleconference, an interim report on progress on enrolling prescribers would be reasonable after 120 days following approval of the REMS modification.

5 Recommendations for the Review Division

We recommend that, instead of requiring an additional full REMS assessment report at a mid-point between the approval of the REMS modification and the next scheduled REMS assessment report, due June 2012, the sponsor be required to report on their progress in enrolling prescribers as of 120 days following approval of the REMS modification. The requirement should be accompanied with a due date for submission of this progress report; e.g., March 1, 2012. The Sponsor can be notified of this additional reporting requirement via the labeling supplement approval letter, or in a letter closing out the REMS assessment report.

We have responded to embedded comments from the sponsor within the REMS and REMS Supporting Document. Please request that the sponsor respond by Wednesday, September 7.

Appended to this review are the proposed REMS, REMS materials, and REMS Supporting Document including our tracked changes.

6 Comments for Alexion

The comments below are based on FDA's review of the REMS modification proposal for Soliris. Additional changes might be needed as the REMS modification undergoes additional review within the FDA.

We have responded to your comments and questions, embedded in the revised documents.

We agree with the revisions to the Soliris Patient Safety Card.

We agree with the consolidation of the Prescriber Introductory Letter and the Prescriber Enrollment Form.

The REMS materials, including the e-capable prescriber enrollment form, should be housed within a REMS-dedicated webpage that can be reached from www.Soliris.net. The REMS-dedicated webpage should be a final destination; that is, once in the REMS-dedicated webpage, the user should be able to access only REMS materials, and should not be able to access marketing materials. Screen shots of the REMS web landing page should be submitted, and the website landing page should be appended to the REMS. See our revision to REMS ETASU B to incorporate this standard.

The Soliris REMS landing page should include links to the Prescribing Information, Medication Guide and Important Safety Information at the top of the page.

There should also be clearly labeled tabs or separate hyperlinks prominently displayed on the webpage to the REMS materials (Prescriber Introductory Letter and Enrollment Form, Prescriber Safety Brochure, Soliris Patient Safety Card, Patient Safety Brochure, and Dosing and Administration Guide) that are part of the Soliris REMS program.

We recommend the following language as background information on the REMS landing page:

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

The goals of the Soliris REMS are:

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To inform and educate Healthcare Professionals (HCP) and Patients (or Caregivers, or Legal Guardians) 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.

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Soliris with attached materials and the REMS Supporting Document. Provide a WORD document with tracked changes and a clean WORD version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate WORD documents.

Format Request: Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

7 Attachments

REMS and REMS Supporting Document

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

DRISK INTERIM REMS REVIEW

REMS Comments Set #1

Date: August 19, 2011

To: Ann Farrell, M.D., Director
Division of Hematology Products (DHP)

Through: Claudia Karwoski, Pharm.D., Director
Division of Risk Management (DRISK) *Claudia Karwoski*
8/22/11

From: **Scientific Lead**, Risk Management Analyst (RMA) *J. Weaver*
Joyce Weaver, Pharm.D., DRISK 8/22/2011

Team Leader, Cynthia LaCivita, Pharm.D., DRISK

DRISK Review Team

Kate Heinrich, M.A., Health Communications Analyst
Therese Cvetkovich, M.D., Clinical Reviewer

Subject: Interim REMS Review Comments Set 1 for Soliris
(eculizumab)

Drug Name (Established Name): Soliris (eculizumab)

Therapeutic Class: Complement Inhibitor

Dosage and Route: Dose varies by indication, age, and weight;
administered by intravenous infusion

Application Type/Number: BLA 125166

Applicant: Alexion

OSE RCM #: 2011-1313

Tracked Safety Issue: 000611

1 Materials Reviewed

- Proposed REMS modification submitted March 25, 2011
- June 1, 2011 Soliris REMS Assessment covering October 2010-March 2011

2 Introduction and Background

Soliris was approved for marketing March 16, 2007 for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. Soliris causes patients receiving the product to be at increased risk for infections, including meningitis, with *Neisseria meningitidis*. Although never approved by the FDA, Alexion had put risk mitigation measures into effect when Soliris was approved for marketing. A REMS was approved for Soliris June 4, 2010 to mitigate the risks of infection with *Neisseria meningitidis* and to mitigate the outcomes for other serious infections, and the risk of discontinuation hemolysis. The REMS is comprised of a Medication Guide, elements to assure safe use (“Healthcare providers who prescribe Soliris are specially certified and patients are monitored for adverse events”), and a Timetable for Submission of Assessment (every 6 months for 1 year, then annually).

The sponsor submitted a labeling supplement March 25, 2011 for the treatment of atypical hemolytic uremic syndrome (aHUS). A REMS modification was submitted to include the new proposed indication.

The sponsor submitted a REMS assessment report on June 1, 2011. The report shows that only about (b) (4)% of current prescribers are registered in the REMS. The report was reviewed by Dr. Therese Cvetkovich, DRISK Clinical Reviewer. Dr. Cvetkovich made the following concluding points in her July 28, 2011 review of the REMS assessment report:

- Prescriber enrollment/certification is central to the Soliris REMS; all active prescribers should be enrolled. Non-PNH (and once approved, non-aHUS) prescribers should be enrolled into the REMS; they should be providing the same risk information to their patients, regardless of underlying diagnosis. The applicant should provide their plans to ensure the enrollment of all prescribers.
- Documentation of presentation of the Patient Safety Card should be incorporated in the “Soliris Adverse Event/Events of Interest Questionnaire” form.

3 Summary of Applicant’s Proposed REMS

The elements of the REMS remains unchanged; that is, the proposed REMS is comprised of a Medication Guide, elements to assure safe use (“Healthcare providers who prescribe Soliris are specially certified and patients are monitored for adverse events”), and a Timetable for Submission of Assessment (every 6 months for 1 year, then annually). The sponsor modified the REMS materials to include the indication under review, the treatment of aHUS.

4 Discussion

An FDA-conducted inspection of the REMS found that the sponsor has not been successful in enrolling prescribers who had prescribed Soliris before the REMS was put into place. Additionally, it appears that enrollment is not being accomplished consistently for new prescribers since the REMS requiring enrollment was put into place. The sponsor has stated to FDA inspectors that they have not been successful enrolling prescribers in the REMS because prescribers regard enrollment as too burdensome. It is clear that the sponsor makes the product available to prescribers despite the failure to enroll the prescribers. Alexion's Soliris website does not state that enrollment in the REMS is required to prescribe Soliris. This information should be included on the Soliris website.

Adding an option to complete facilitated enrollment via phone, and linking access to Soliris to the enrollment (linked access is supposed to be in place currently), might help the sponsor achieve full prescriber enrollment in the REMS. We propose to incorporate this change in the enrollment process. This proposal will be discussed with the sponsor during a teleconference scheduled for August 22.

After a discussion of the REMS assessment report on July 25, 2011, that included a discussion of the data regarding serious infections and discontinuation hemolysis, DHP and DRISK agreed that the REMS should be modified to focus on the risk of meningococcal infection. Discontinuation hemolysis, a theoretical risk included in the approved REMS, has not surfaced to date. DRISK agrees that this risk can be removed from the REMS. Likewise, the development of other serious infections is theoretical, and it is not possible to determine causality with case reports in the at-risk patient population receiving Soliris. DRISK agrees that this risk can also be removed from the REMS.

5 Recommendations for the Review Division

DHP and DRISK agreed that the changes needed in the REMS as a result of the deficiencies found in the REMS assessment report can be accomplished with the REMS modification currently being considered in conjunction with the new indication. We drafted changes to the proposed REMS document and REMS Supporting Document submitted with the modification to accomplish the following:

- Incorporate an optional streamlined prescriber enrollment via phone
- Remove the risk of other severe infections from the REMS
- Remove discontinuation hemolysis from the REMS

Additional changes to the documents were needed for consistency with FDA modifications to the proposed labeling. The necessary changes are in track changes in the REMS and REMS Supporting Document (attached).

We recommend that the following comments on the Soliris REMS proposal be sent to the applicant. Please request that the applicant respond to these comments within 7 days.

Appended to this review are the proposed REMS, REMS materials, and REMS Supporting Document including our tracked changes.

6 Comments for Alexion

The comments below are based on FDA's initial review of the REMS modification proposal for Soliris. Additional changes might be needed as the REMS modification undergoes additional review within the FDA.

Based upon draft modification of the Soliris PI to to remove discontinuation hemolysis and other serious infections from the adverse event sections, we have made revisions to the REMS and REMS Supporting Document showing the necessary changes. We made additional changes to the REMS for consistency with the current draft labeling. Please make the requested changes and return within 7 days.

The REMS materials (Soliris Patient Safety Card, Prescriber Introductory Letter, Patient Safety Brochure, *Important Safety Information about Soliris*, Prescriber Safety Brochure, *Important Safety Information about Soliris*, Prescriber Enrollment Form, Dosing and Administration Guide) should be attached directly to the REMS document. The materials may be included in the REMS Supporting Document as well.

We drafted suggested changes to the survey instruments [REDACTED] (b) (4)

[REDACTED]. Submit the methodology and survey instrument(s) for review at least 90 days before the next evaluation is conducted. Submit both methods and instruments together.

We note that your product website does not state that enrollment in the REMS is required to prescribe Soliris. This information should be included on the Soliris website.

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Soliris with attached materials and the REMS Supporting Document. Provide a WORD document with tracked changes and a clean WORD version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate WORD documents.

Format Request: Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single WORD document. If certain

documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

7 Attachments

REMS and REMS Supporting Document

64 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125166s172

REMS

Initial REMS Approval: 6/4/2010
Most Recent Modification: 9/21/2011

BLA 125166 Soliris® (eculizumab)
Recombinant Humanized Monoclonal Antibody

Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410

(203) 272-2596

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S)

The goals of the REMS are:

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

II. REMS ELEMENTS

A. Medication Guide

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

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

B. Elements to Assure Safe Use

Healthcare providers who prescribe Soliris are specially certified.

- a. Prescriber certification is based on prescriber agreement that the prescriber will:
 - i) Counsel patients and provide the patient educational materials to the patient, including the Soliris Patient Safety Card and the Medication Guide
 - ii) Provide the Medication Guide to the patient prior to each infusion
 - iii) Review the educational materials (Soliris Patient Safety Card, Prescriber Introductory Letter, Prescriber Safety Brochure, *Important Safety Information about Soliris*, Patient Safety Brochure, *Important Safety Information about Soliris*, and Dosing and Administration Guide) and the product labeling and comply with the directions for safe use including ensuring patients receive a meningococcal vaccine.
 - iv) Promptly report to the Sponsor at 1-888-765-4747 or to the FDA at 1-800-332-1088 cases of meningococcal infection, including the patients' clinical outcomes
- b. The prescriber will fax the completed enrollment form to 1-877-580-2596 (ALXN), email the completed form to OSSP@alxn.com, or mail the form to Alexion at Alexion Pharmaceuticals, 352 Knotter Drive, Cheshire, CT 06410, Attn: OneSource Safety Support Program.

A prescriber may also complete the enrollment by phone with Alexion at 1-888-765-4747 or electronically via the Soliris REMS website at www.soliris.net

- c. Alexion will contact certified prescribers annually and provide the educational materials (Medication Guide, Soliris Patient Safety Card, Prescriber Safety Brochure, *Important Safety Information about Soliris*, Patient Safety Brochure, *Important Safety Information about Soliris*, and Dosing and Administration Guide). The educational materials and enrollment form will be available on a REMS-dedicated webpage accessible from www.soliris.net.
- d. The following materials are part of the REMS and are appended
 - (1) Soliris Patient Safety Card
 - (2) Prescriber Introductory Letter and Enrollment Form
 - (3) Patient Safety Brochure, *Important Safety Information about Soliris*
 - (4) Prescriber Safety Brochure, *Important Safety Information about Soliris*
 - (5) Dosing and Administration Guide
 - (6) REMS website
- e. Alexion will maintain a database of certified prescribers in the REMS program, and will ensure that Soliris is distributed only to certified prescribers. Alexion will ensure that prescribers comply with the requirements of the REMS Program.

C. Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA every six months for one year, and then annually thereafter from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Alexion will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDICES

The following documents are appended:

- (1) Soliris Patient Safety Card
- (2) Prescriber Introductory Letter and Enrollment Form
- (3) Patient Safety Brochure, *Important Safety Information about Soliris*
- (4) Prescriber Safety Brochure, *Important Safety Information about Soliris*
- (5) Dosing and Administration Guide
- (6) REMS website (screenshots)

Appendix 1
Soliris Patient Safety Card

PATIENT SAFETY INFORMATION CARD



Important Safety Information for Patients Taking Soliris®

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

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever of 103°F (39.4°C) or higher
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light



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

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

PATIENT SAFETY INFORMATION CARD

+ Information for the Treating Physician



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

- Meningococcal infections may 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).

+ 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[®]
(e c u l i z u m a b)

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Appendix 2
Prescriber Introductory Letter and Enrollment Form

Dear Soliris® (eculizumab) Prescriber,

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

To get started in the Program, please complete the Prescriber Enrollment Form on the reverse side and either drop it in the mail; fax it to the Soliris OneSource Safety Support Program at 1.877.580.2596 (ALXN); or scan and e-mail it to OSSP@alxn.com.

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

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

I agree to:

- Review the product labeling and educational materials, and comply with the safety instructions for use, including ensuring meningococcal vaccination status
- Counsel patients (or caregivers, or legal guardians) and provide educational materials to the patient (or caregivers, or legal guardians), including the Soliris Patient Safety Information Card, and the Soliris Medication Guide
- Intend to promptly report cases of meningococcal infection, including the patient's clinical outcomes, by contacting the OneSource Safety Support Program (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 www.fda.gov/medwatch
- Revaccinate patients in accordance with the Advisory Committee on Immunization Practices (ACIP) recommendations for the duration of Soliris therapy

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected

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

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

INDICATIONS AND USAGE

Soliris is a complement inhibitor indicated for:

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

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

CONTRAINDICATIONS

Soliris is contraindicated in:

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥15% combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

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

Name (printed): _____

Signature: _____

Date: _____

Title: _____

Office Address: _____

E-mail: _____

City: _____

State: _____

ZIP: _____

Country: _____

Phone Number: _____

Fax Number: _____

Appendix 3

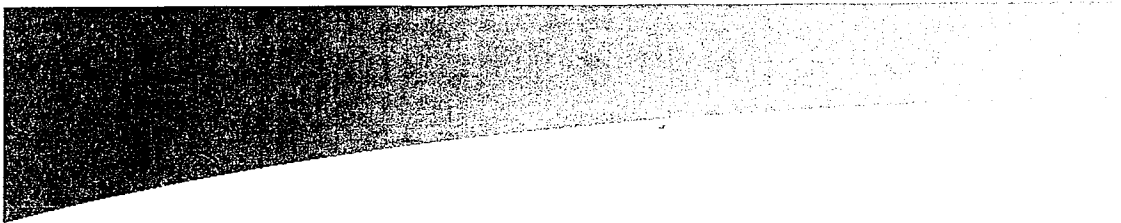
Patient Safety Brochure, *Important Safety Information about Soliris*

Before starting on Soliris®.

Important safety information for patients



SOLIRIS®
(eculizumab)



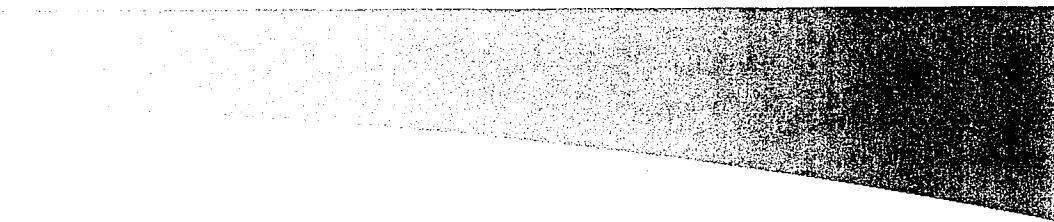
Before you begin Soliris® (eculizumab) treatment, your physician will give you a:

- Medication Guide
- Soliris Patient Safety Information Card

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

2

Please see back cover for Important Safety Information.
Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.



Patient Safety Information Card

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

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

PATIENT SAFETY INFORMATION CARD



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

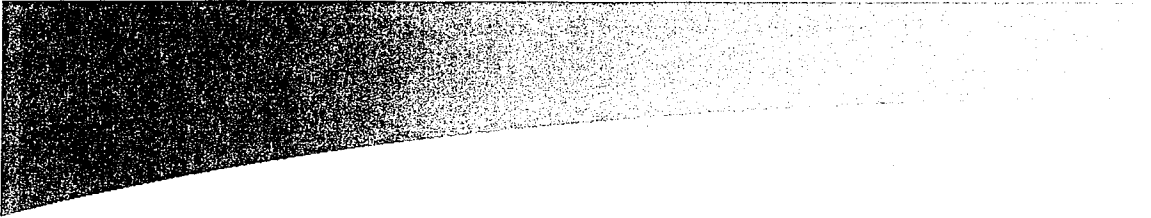
Soliris OneSource™ Treatment Support Program

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

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

SOLIRIS®
(eculizumab)

3



For Discussion With Patients— Important Safety Information

MEDICATION GUIDE

Soliris® (so-leer-is) (eculizumab)

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

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

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

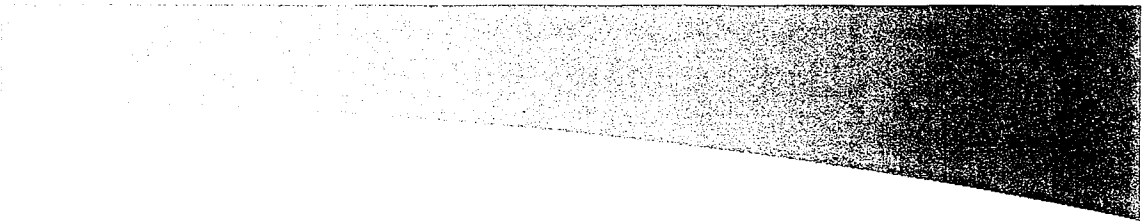
- Soliris increases your risk of getting serious and life-threatening meningococcal infections

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

1. You must receive a meningococcal vaccine at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decides that urgent treatment with Soliris is needed, you should receive a meningococcal vaccine as soon as possible.
2. If you had a meningococcal vaccine in the past, you might need a booster dose before starting Soliris. Your doctor will decide if you need another dose of a meningococcal vaccine.
3. A meningococcal vaccine does not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:

— headache with nausea or vomiting	— fever and a rash
— headache and a fever	— confusion
— headache with a stiff neck or stiff back	— muscle aches with flu-like symptoms
— fever of 103°F (39.4°C) or higher	— eyes sensitive to light

Please see back cover for Important Safety Information.
Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.



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

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

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

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

What is Soliris?

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

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). PNH affects red blood cells.
- a disease called atypical Hemolytic Uremic Syndrome (aHUS). aHUS affects the blood system, kidney, and sometimes other body organs.

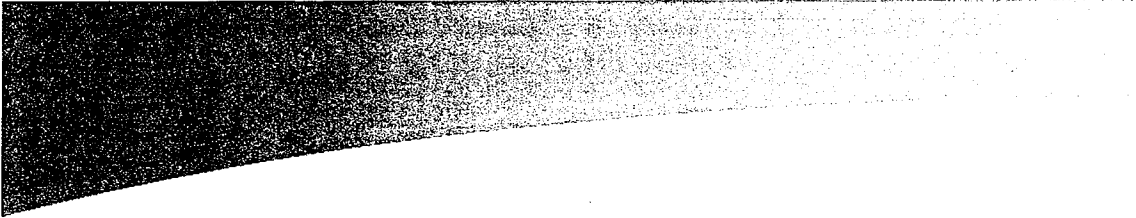
Soliris works by blocking part of your immune system. This can help your symptoms but it can also increase your chance for infection.

It is important that you:

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

SOLIRIS[®]
(eculizumab)

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For Discussion With Patients— Important Safety Information (continued)

Who should not receive Soliris®?

Do not receive Soliris if you:

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

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if you:

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

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

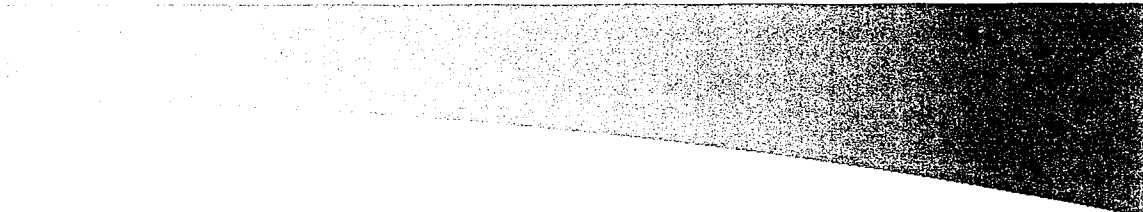
Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes. If you have an allergic reaction during your Soliris infusion, your doctor may decide to give Soliris more slowly or stop your infusion.
- If you are an adult, you will usually receive a Soliris infusion by your doctor:
 - weekly for five weeks, then
 - every 2 weeks
- If you are less than 18 years of age, your doctor will decide how often you will receive Soliris depending on your age and body weight.
- After each infusion, you should be monitored for one hour for allergic reactions. See “What are the possible side effects of Soliris?”
- If you forget or miss a Soliris infusion, call your doctor right away.

Please see back cover for Important Safety Information.

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

- 
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris®. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**

Symptoms or problems that can happen due to red blood cell breakdown include:

- drop in the number of your red blood cells
- drop in your platelet count
- confusion
- chest pain
- kidney problems
- blood clots
- difficulty breathing

- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

Symptoms or problems that can happen with abnormal clotting may include:

- stroke
- confusion
- seizures
- chest pain (angina)
- difficulty breathing
- kidney problems
- swelling in arms or legs
- a drop in your platelet count

What are the possible side effects of Soliris?

Soliris can cause serious side effects, including:

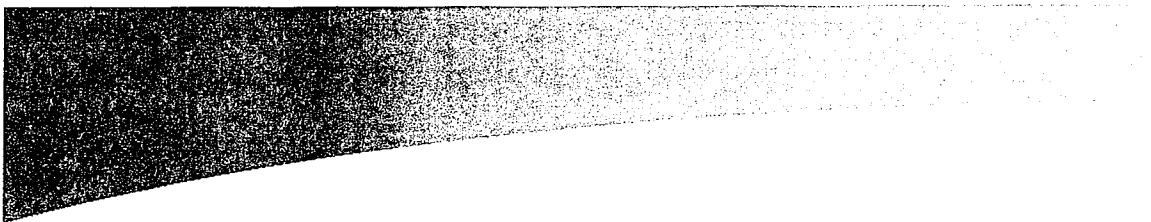
- **See “What is the most important information I should know about Soliris?”**
- **Serious allergic reactions.** Serious allergic reactions can happen during your Soliris infusion. Tell your doctor or nurse right away if you get any of these symptoms during your Soliris infusion:

- chest pain
- trouble breathing or shortness of breath
- swelling of your face, tongue, or throat
- feel faint or pass out

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

SOLIRIS[®]
(eculizumab)

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For Discussion With Patients— Important Safety Information (continued)

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

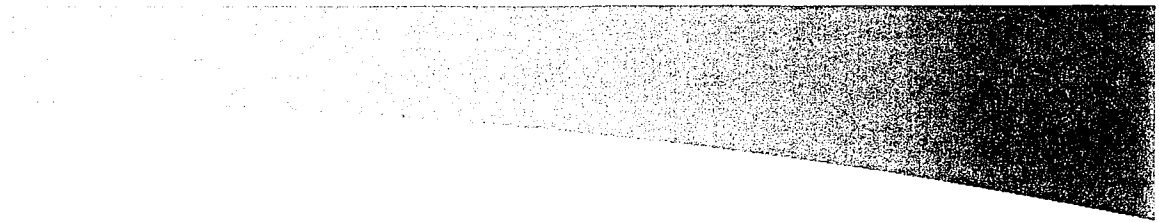
- headaches
- runny nose and colds
- sore throat
- back pain
- nausea

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

- high blood pressure
- common cold (upper respiratory infection)
- diarrhea
- headache
- nausea and vomiting
- low red blood cell count
- low white blood cell count
- urinary tract infection

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 Soliris®

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

What are the ingredients in Soliris?

Active ingredient: eculizumab

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

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

Manufactured by Alexion Pharmaceuticals, Inc.
352 Knotter Drive, Cheshire, CT 06410 USA.

Revised: 09/2011

SOLIRIS®
(eculizumab)

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Want to learn more about Soliris®?

- Visit www.Soliris.net
- Call 1.888.SOLIRIS (1.888.765.4747)

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected

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

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

The most frequently reported adverse reactions in aHUS single arm prospective trials ($\geq 15\%$ combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

ALEXION

SOLIRIS®
(eculizumab)

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

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All rights reserved. SOL-1138

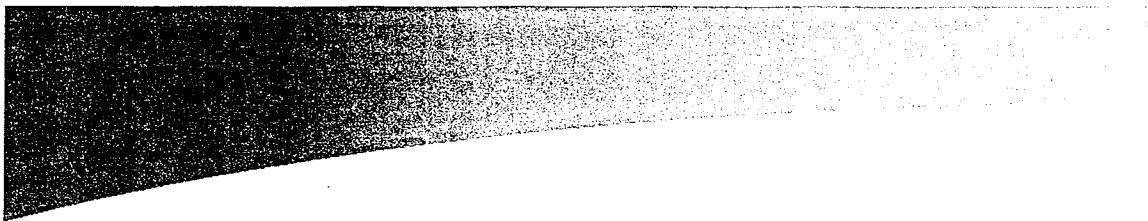
Appendix 4

Prescriber Safety Brochure, *Important Safety Information about Soliris*

Before starting your patients on Soliris®.

Important safety information for the healthcare provider

SOLIRIS®
(eculizumab)



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

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

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

2

Please see back cover for Important Safety Information.
Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.

Patient Safety Information Card

You are provided with Patient Safety Information Cards to give to your patients. You should discuss the importance and the proper use of this card with every patient.

Patients should carry this card at all times to show to any healthcare professional involved in their care. The Patient Safety Information Card contains safety guidance for Soliris patients and their healthcare providers.

Prescribers should advise patients to seek medical attention immediately if they develop headache with nausea or vomiting, or headache and fever, even if they don't have their Patient Safety Information Card with them.

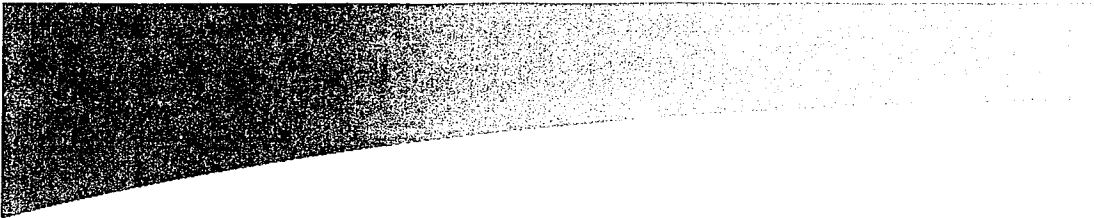
PATIENT SAFETY INFORMATION CARD



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

SOLIRIS®
(eculizumab)

3



For Discussion With Patients— Important Safety Information

MEDICATION GUIDE

Soliris® (so-leer-is) (eculizumab)

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

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

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

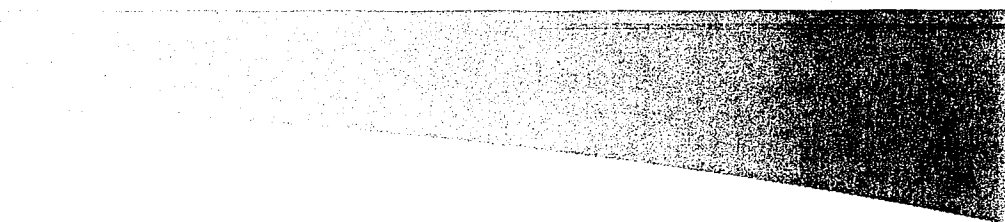
- Soliris increases your risk of getting serious and life-threatening meningococcal infections.

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

1. You must receive a meningococcal vaccine at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decides that urgent treatment with Soliris is needed, you should receive a meningococcal vaccine as soon as possible.
2. If you had a meningococcal vaccine in the past, you might need a booster dose before starting Soliris. Your doctor will decide if you need another dose of a meningococcal vaccine.
3. A meningococcal vaccine does not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:

— headache with nausea or vomiting	— fever and a rash
— headache and a fever	— confusion
— headache with a stiff neck or stiff back	— muscle aches with flu-like symptoms
— fever of 103°F (39.4°C) or higher	— eyes sensitive to light

Please see back cover for Important Safety Information.
Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.



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

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

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

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

What is Soliris?

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

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). PNH affects red blood cells.
- a disease called atypical Hemolytic Uremic Syndrome (aHUS). aHUS affects the blood system, kidney, and sometimes other body organs.

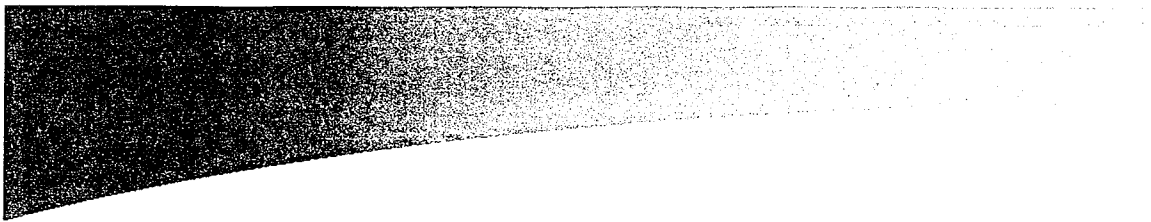
Soliris works by blocking part of your immune system. This can help your symptoms but it can also increase your chance for infection.

It is important that you:

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

SOLIRIS[®]
(eculizumab)

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For Discussion With Patients— Important Safety Information (continued)

Who should not receive Soliris®?

Do not receive Soliris if you:

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

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if you:

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

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

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

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes. 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?”

Please see back cover for Important Safety Information.

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

- If you forget or miss a Soliris® infusion, call your doctor right away.
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**

Symptoms or problems that can happen due to red blood cell breakdown include:

- drop in the number of your red blood cells
- drop in your platelet count
- confusion
- chest pain
- kidney problems
- blood clots
- difficulty breathing

- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

Symptoms or problems that can happen with abnormal clotting may include:

- stroke
- confusion
- seizures
- chest pain (angina)
- difficulty breathing
- kidney problems
- swelling in arms or legs
- a drop in your platelet count

What are the possible side effects of Soliris?

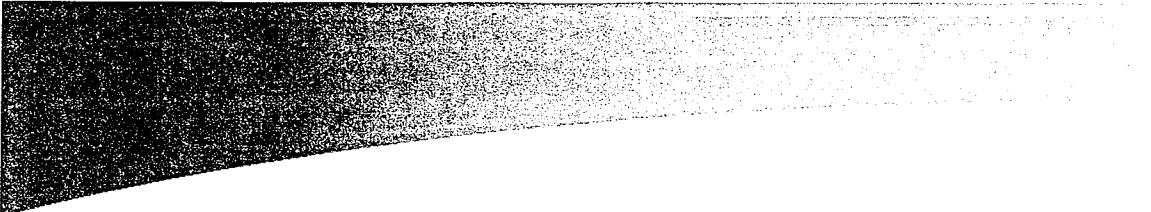
Soliris can cause serious side effects, including:

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

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

SOLIRIS®
(eculizumab)

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For Discussion With Patients— Important Safety Information (continued)

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

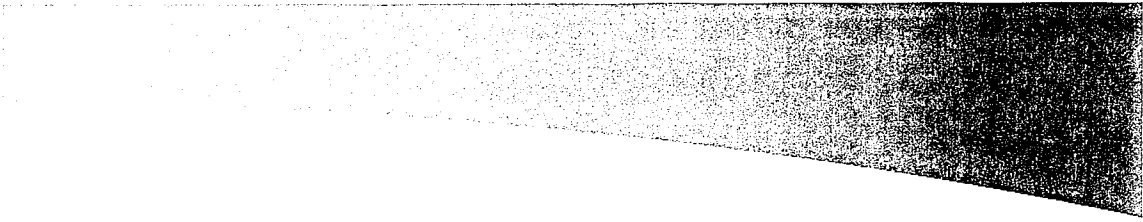
- headaches
- runny nose and colds
- sore throat
- back pain
- nausea

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

- high blood pressure
- common cold (upper respiratory infection)
- diarrhea
- headache
- nausea and vomiting
- low red blood cell count
- low white blood cell count
- urinary tract infection

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 Soliris®

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

What are the ingredients in Soliris?

Active ingredient: eculizumab

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

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

Manufactured by Alexion Pharmaceuticals, Inc.
352 Knotter Drive, Cheshire, CT 06410 USA.

Revised: 09/2011

**SOLIRIS®**
(eculizumab)

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Want to learn more about Soliris®?

- Visit www.Soliris.net
- Call 1.888.SOLIRIS (1.888.765.4747)

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected

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

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

The most frequently reported adverse reactions in aHUS single arm prospective trials ($\geq 15\%$ combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

ALEXION

SOLIRIS®
(ecm122umab)

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Appendix 5
Dosing and Administration Guide

SOLIRIS[®]
(eculizumab)

For Paroxysmal Nocturnal Hemoglobinuria
(PNH) and atypical Hemolytic Uremic
Syndrome (aHUS) patients

PNH | aHUS

Dosing and Administration

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.

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

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

ONESOURCE[™]
TREATMENT SUPPORT

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

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

Indications and usage

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

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

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Progressive clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of use

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

Adverse reactions

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

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥15% combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and neuropathy.

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

For patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Soliris® (eculizumab) PNH Dosing Guide

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

Soliris, a chronic therapy for a chronic disease!²

Pre-treatment	PNH Dosing Schedule for Patients >16 years									
	To the 1st Phase					From the 1st Phase				
12 weeks	1	2	3	4	5	6	7	8	9	10
At least 2 weeks prior to first dose	600 mg	600 mg	600 mg	600 mg	900 mg	900 mg	900 mg	900 mg	900 mg	900 mg

12 weeks prior to first dose of the recommended dosage regimen, then once, or twice, for the first 12 weeks post-treatment.

- Soliris should be administered at the recommended dosing schedule or within 2 days before or after these time points.

- Fixed dose on time is critical to control chronic, complement-mediated hemolysis. An breakthrough hemolysis, dosing may be adjusted to every 12 days instead of 14 days³
- No dosing adjustments recommended based on age, gender, race, or renal insufficiency⁴
- Pre-medications are not routinely required



Monitoring After Discontinuation

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

Important Administration Information

Soliris must be diluted to a final admixture concentration of 5 mg/mL prior to administration.

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

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

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

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

SOLIRIS®
(eculizumab)

For patients with atypical Hemolytic Uremic Syndrome (aHUS)
Soliris® (eculizumab) aHUS Dosing Guide

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

Soliris is a therapy for aHUS—a chronic disease needing chronic treatment†

Pre-treatment		Induction Phase				Maintenance Phase			
22 weeks before initiation	White	1	2	3	4	5	6	7	8
At least 2 weeks before initiation	Soliris	900 mg	900 mg	900 mg	900 mg	1200 mg	1200 mg	1200 mg	1200 mg
	injection	q14d	q14d	q14d	q14d	q2w	q2w	q2w	q2w

Body Weight	Induction Phase	Maintenance Phase
40 kg and over	900 mg weekly x 4 doses	1200 mg at week 5, then 1200 mg every 2 weeks
33 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3, then 900 mg every 2 weeks
25 kg to less than 33 kg	600 mg weekly x 2 doses	600 mg at week 3, then 600 mg every 2 weeks
18 kg to less than 25 kg	600 mg weekly x 1 dose	600 mg at week 2, then 300 mg every 2 weeks
5 kg to less than 18 kg	300 mg weekly x 1 dose	300 mg at week 2, then 300 mg every 2 weeks

→ Soliris should be administered at the recommended dosing interval or within 2 days before or after these time points.



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

Supplemental dosing of Soliris is required for patients undergoing concomitant plasma therapy†

Type of Intervention	Most Recent Soliris Dose	Supplemental Soliris Dose With Each PCPT Intervention	Timing of Supplemental Soliris Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	600 mg or more	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	300 mg or more	300 mg per each unit of fresh frozen plasma	60 minutes prior to each 1 unit of fresh frozen plasma infusion

†PCPT = plasmapheresis or plasma exchange, or both (see plasma infusion).

Monitoring After Discontinuation

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

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

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

- If diluted solution is refrigerated, warm to room temperature (18°C-25°C (64°F-77°F)) only by exposure to ambient air.
- Administer as an IV infusion over 35 minutes via gravity†, a syringe-type pump, or an infusion pump.
- It is not necessary to protect diluted solution from light during administration.

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

†Plasma therapy = plasmapheresis, plasma exchange, or both (see plasma infusion).

aHUS Dosing

SOLIRIS®
(eculizumab)

For PNH and aHUS

Preparation of Soliris® (eculizumab) for Administration¹

All patients must be vaccinated against *Neisseria meningitidis* at least 2 weeks prior to the first dose of Soliris therapy. Do not initiate Soliris therapy in patients with unresolvent 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.²

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

1. Withdraw the required amount of Soliris from the vial into a sterile syringe and transfer the recommended dose to an infusion bag.
2. Dilute Soliris to a final concentration of 5 mg/mL using the above table as a guideline. The volume of diluent should be equivalent to the drug volume.
3. Gently invert the infusion bag containing the diluted solution to ensure thorough mixture of the product and the diluent.
 - Discard any unused portion left in the vial, as the product contains no preservatives.
4. Inspect visually for particulate matter and discoloration prior to administration.
 - The diluted solution is a clear colorless liquid and should be practically free of any particles.
5. Allow the solution to adjust to room temperature prior to administration (15°C-25°C, 54°F-77°F). It must not be heated in a microwave or with any heat source other than ambient air temperature.
6. Administer solution of Soliris is stable for 24 hours at 2°C-8°C (36°F-46°F) and at room temperature.

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

How Supplied/Storage and Distribution¹

- Vial—30 mL, liquid
- Product strength—10 mg/mL
- Product count—300 mg/30 mL (vial)
- Product physical specs—1 vial per carton
 - Shipped just in time for infusion
 - Weight: <1 lb
 - Dimensions: 1.625" x 1.625" x 3.125"
- Must be stored in the original carton until time of use under conditions at 2°C-8°C (36°F-46°F)
- Protect from light
- DO NOT FREEZE; DO NOT SHAKE
- Do not use beyond the expiration date stamped on the carton
- NDC 25682-001-01: Each single-unit carton contains one 30-mL vial of Soliris (10 mg/mL)



→ To enroll in the Soliris REMS and order Soliris, please call 1.888.SOLIRIS (1.888.765.4747)

Diagnosis code: XXXXXX
J code: J1300
Procedure code: XXXXXXX



Contact Soliris OneSource at 1.888.SOLIRIS (1.888.765.4747)

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

SOLIRIS
(eculizumab)

Storage and Distribution

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

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

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

References: 1. Soliris® [package insert]. Cheshire, CT: Alexion Pharmaceuticals, Inc; 2011. 2. Helley D, de Latour RP, Pocher R, et al, French Society of Hematology. Evaluation of hemostasis and endothelial function in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. *Haematologica*. 2010;95:574-581.

ALEXION

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Appendix 6
REMS website (screenshots)

Soliris REMS Information - Windows Internet Explorer
http://solirisrems-staging/index.html

Home | [Prescribing Information](#) | [Medication Guide](#) | [Important Safety Information](#)

ONESOURCE™ SAFETY SUPPORT

Increased Risk of Meningococcal Infection and Soliris: Risk Evaluation and Mitigation Strategy (REMS)

Prescribers must enroll in the Soliris REMS to prescribe Soliris.

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

The goals of the Soliris REMS, the OneSource Safety Support Program, are:

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To inform and educate Healthcare Professionals (HCP) and Patients (or Caregivers, or Legal Guardians) 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.

Physicians prescribing Soliris must enroll in the REMS.

To enroll in the program, download and complete the Prescriber Introductory Letter and Enrollment Form and either drop it in the mail; fax it to Soliris OneSource Safety Support Program at 1-877-580-2596 (ALXN); or scan and e-mail it to OSSP@alxn.com.

- [Prescriber Introductory Letter and Enrollment Form](#)
- [Patient Introductory Letter and Voluntary Enrollment Form](#)
- [Dosing and Administration Guide](#)
- [Soliris Patient Safety Card](#)
- [Prescriber Brochure, Important Safety Information about Soliris](#)
- [Patient Safety Brochure, Important Safety Information about Soliris](#)

The Soliris Patient Safety Card

Provide your patient with a Soliris Patient Safety Card to carry with them at all times. This safety card contains important safety information about the risk of meningococcal infection that your patient needs to be aware of before they are given Soliris and during their treatment with Soliris. Remind them to show this card to any doctor involved in their treatment.

Tell your patients that if they cannot reach their doctor, go to an emergency room immediately and show emergency room staff the Soliris Patient Safety Card. *Even if they stop using Soliris*, patients should keep their Soliris Patient Safety Card with them for 3 months after the last Soliris dose, since side effects may occur a long time after their last dose of Soliris.

To order a Soliris Patient Safety Information Card, contact OneSource™ at 1.888.SOLIRIS (1.888.765.4747).





Home [Prescribing Information](#) [Medication Guide](#) [Important Safety Information](#)

Important Safety Information

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning.

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with a meningococcal vaccine 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 Serious Meningococcal Infections for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

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

INDICATIONS AND USAGE

Paroxysmal Nocturnal Hemoglobinuria (PNH)

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

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.

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

CONTRAINDICATIONS

Soliris is contraindicated in:

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

WARNINGS AND PRECAUTIONS

Other Infections

Soliris blocks terminal complement activation, therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. 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.

Monitoring After Soliris Discontinuation

Treatment Discontinuation for PNH

Monitor patients after discontinuing Soliris for at least 6 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 studies, 16 patients (5 in the prospective studies) discontinued Soliris treatment. TMA complications occurred following a missed dose in 5 patients, and Soliris was restarted 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 (FFPI)], or appropriate organ-specific supportive measures.

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.

Laboratory Monitoring

PNH

Serum LDH levels increase during hemolysis and may assist in monitoring Soliris effects, including the response to discontinuation of therapy. In clinical studies, all patients achieved a reduction in serum LDH levels only after a decrease in the Soliris dosing interval from 7 to 12 days. All other patients achieved a reduction in serum LDH levels with the 14 day dosing interval [see *Clinical Pharmacology and Clinical Studies*].

aHUS

Early signs of thrombotic microangiopathy (TMA) include a decrease in platelet count, and increases in serum LDH and creatinine levels. Follow patients for signs of TMA by monitoring serial platelet counts, serum LDH, and creatinine during Soliris therapy and following discontinuation of Soliris.

Infusion Reactions

As with all protein products, 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 initiate appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

ADVERSE REACTIONS

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

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥15% combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leiomyoma.

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

NEW SUPPLEMENT FOR BLA 125166 SOLIRIS[®] (eculizumab)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

SUPPORTING DOCUMENT

Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410

Sept 21, 2011

Reference ID: 3168294

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OUTLINE OF THE RISK EVALUATION AND MITIGATION STRATEGY FOR SOLIRIS

Alexion Pharmaceuticals, Inc. is submitting an updated Risk Evaluation and Mitigation Strategy for Soliris® (eculizumab). In this submission, this REMS program will be referred to as “OneSource Safety Support Program”, although the OneSource Safety Support Program actually encompasses more than the REMS; for example, the patient registry. This section of the submission briefly outlines the various components of the OneSource Safety Support Program and will reference all documents which will be included in the submission. It will also provide an overview of the communication plan and the resources which will be required for the implementation of this program. In this document, the Soliris Specialists will be comprised of the Alexion Nurse Case Manager at OneSource as well as Alexion field representatives. The OneSource Safety Support Program will remain in effect as long as the drug is made commercially available in the United States by Alexion Pharmaceuticals, Inc.

ONESOURCE SAFETY SUPPORT PROGRAM INFORMATION BACKGROUND

Soliris was approved on March 16, 2007 for the treatment of patients with PNH to reduce hemolysis. At that time, Alexion Pharmaceuticals, Inc. agreed to implement a Risk Minimization Action Plan (RiskMAP) which primarily focused on three important safety risks which were identified during the development of Soliris. Specifically meningococcal infections, serious infections, and serious hemolysis following treatment discontinuation were important potential safety issues for patients receiving Soliris. Although these risks could not be prevented, the use of a meningococcal vaccine as well as physician and patient education were identified as important ways to mitigate the risk. The RiskMAP which was put in place led to the implementation of a number of important measures listed below. Physician and patient awareness through:

- Package insert / Medication Guide
- Boxed Warning for Meningococcal Infection
- Warning and Precaution for Meningococcal Infection
- Warning and Precaution for Systemic Infections
- Distribution of education materials to HCPs and patients
- Patient Safety Card
- Ongoing patient education through OneSource
- Awareness and monitoring
 - Vaccination with a meningococcal vaccine
 - Revaccination per manufacturer's recommendation
 - Awareness of early signs of meningococcal infection
 - Monitoring for possible serious hemolysis after Soliris discontinuation
- Reporting and evaluation tools
 - Soliris Safety Observation Program
 - HCP and Patients Survey

1. PROGRAM OUTLINE

1.1 Goals

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To inform and educate Healthcare Professionals (HCP) and Patients (or Caregivers, or Legal Guardians) 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.

1.2 REMS Elements

1.2.1 Soliris Medication Guide

The Medication Guide will be distributed to HCPs and patients (or Caregivers, or Legal Guardians) using the following procedures

- General:
 - The Medication Guide is currently distributed with the package insert and delivered with each vial of Soliris
 - The Medication Guide is available by fax, mail and the internet at www.Soliris.net as well as through OneSource at 1-888-SOLIRIS
- Healthcare Providers:
 - The Medication Guide will be distributed to HCPs
 - A Soliris Specialist will review the Medication Guide with HCPs
- Patients, or Caregivers, or Legal Guardians:
 - HCPs will provide each patient (or caregiver or legal guardian) with the Soliris Medication Guide prior to the initiation of Soliris treatment
 - A Soliris Specialist will review the Medication Guide with patients, (or caregiver or legal guardian) when they are enrolled in the OneSource Safety Support Program

Please see the Medication Guide (See Section 4.6)

1.2.2 Elements to Assure Safe Use

Educational materials and the Medication Guide will be distributed to HCPs, and Patients, (or Caregivers, or Legal Guardians).

1.2.2.1 Healthcare Provider

Enrollment in the OneSource Safety Support Program requires the Prescriber to attest to the following:

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

- the need for the patient to receive meningococcal vaccination at least 2 weeks prior to beginning Soliris (eculizumab)
- the risk of developing meningococcal infection while receiving Soliris (eculizumab)

I agree to:

- review the product labeling and educational materials and comply with the safety instructions for use including ensuring patients are vaccinated with a meningococcal vaccine
- counsel Patients (or Caregivers, or Legal Guardians) and provide the patient educational materials to the patient (Caregiver or Legal Guardian), including the Soliris Patient Safety Card and the Soliris Medication Guide
- intend to promptly report cases of meningococcal infection, including the patient's clinical outcomes, by contacting Soliris OneSource (Alexion Pharmaceuticals, Inc.) at 1-888-SOLIRIS (1-888-765-4747) or reporting the information to FDA MedWatch Reporting System by phone at 1-800-FDA-1088 (1-800-332-1088) or by mail using Form 3500 at www.fda.gov/medwatch.
- revaccinate according to current Advisory Committee on Immunization Practices (ACIP) medical guidelines for vaccine use.

The Healthcare Prescriber Enrollment Form must be completed and submitted either electronically or faxed to the OneSource Safety Support Program (1-877-580-2596 (ALXN)) or given to a Soliris Specialist who is assigned to you and your patient.

Please see the following appended documents:

- Healthcare Prescriber Introductory Letter and Enrollment Form (See Section 4.1)
- Soliris Medication Guide (See Section 4.6)
- Soliris Patient Safety Card (See Section 4.7)
- Soliris Dosing and Administration Guide (Section 4.10)

1.2.2.2 Patient Enrollment Form

Each patient treated with Soliris should be offered voluntary enrollment in the OneSource Safety Support Program

- I have read this Patient Information Form.

I have had the opportunity to ask my healthcare provider questions regarding important safety information regarding Soliris treatment. I understand the explanations provided.

I understand that I must fulfill my requirements regarding vaccination and revaccination and/or appropriate antibiotic prophylaxis.

My signature indicates that I have read, understood, and agree with all the statements above.

Please see the following appended documents:

- Patient Introductory Letter and Voluntary Enrollment Form (See Section 4.2)
- Soliris Medication Guide (See Section 4.6)
- Soliris Patient Safety Card (See Section 4.7)

Outcome data from patients who enroll in the optional OneSource Safety Support Program

Safety Monitoring: A Soliris Patient Baseline Data Form will be completed for each patient within 30 days of enrolling. Following that, a Soliris Safety Questionnaire will be completed every six months during treatment with Soliris. A Soliris Specialist will remind the HCP when it is time to complete the Soliris safety questionnaire. Forms and questionnaires may be completed and provided to the Soliris OneSource Safety Support Program (Please see Section 4.3, Soliris Safety Observation Program).

- All reported serious adverse events will be investigated as needed by Alexion's Global Pharmacovigilance department or designee.
- Patient Discontinuation: At the time a patient wishes to discontinue Soliris or a prescriber determines that a patient should discontinue Soliris, the prescriber should contact the Soliris Specialist. The Soliris Discontinuation/Post Discontinuation Form must be completed at the time of discontinuation.

Please see the following appended documents:

- Soliris Safety Observation Program
 - Baseline Data Form
 - Safety Questionnaire
 - Soliris Serious Adverse Events/Events of Interest Questionnaire
 - Discontinuation/Post Discontinuation Form Implementation System

The **OneSource Safety Support Program** includes the following:

- The OneSource Safety Support Program will maintain a database of all enrolled Prescribers and patients.
- The OneSource Safety Support Program will monitor the compliance with baseline data collection, safety monitoring, discontinuation and post-discontinuation procedures. If a prescriber is found to be non-compliant with the OneSource Safety

Support Program, Alexion will take the appropriate measures to support the practitioner and regain compliance with the program.

- Based on monitoring and evaluation of the Elements to Assure Safe Use, Alexion will take reasonable steps to improve the compliance with the implementation of these elements as needed.

1.2.3 Timetable for Submission of Assessments

Assessment reports will be submitted to FDA at 6 months, 1 year, and annually thereafter following initial approval of the REMS for as long as the drug is made commercially available in the United States by Alexion Pharmaceuticals, Inc.

Information needed for assessments

OneSource Safety Support Program will include the following information:

- Assessment of enrollment and discontinuation statistics for patients and prescribers
 - The number of patients enrolled in the OneSource Safety Support Program and receiving Soliris treatment (during the reporting period and cumulative)
 - The number of patient person-years for enrolled patients on Soliris
 - The number of new patients enrolled during the reporting period
 - The number of patients who received Soliris who were not enrolled (during the reporting period and cumulative)
 - The number of patients who discontinued Soliris (during the reporting period and cumulative)
 - The number of patients who were lost to follow up (during the reporting period and cumulative)
 - Prescriber enrollment:
 - Numbers enrolled: total and newly enrolled during the reporting period,
 - Number who are prescribing Soliris who are not enrolled
 - Reasons that prescribers did not enroll
 - Actions taken to ensure that all prescribers are enrolled
- An assessment of the following use data for Soliris
 - The number of patients treated by diagnosis
 - The number of pediatric patients
 - The percent of patients receiving meningococcal vaccination
- The number and summary of prescribers who were un-enrolled from the OneSource Safety Support Program during the reporting period and cumulative
- Alexion Global Pharmacovigilance will write a narrative summary and analysis of meningococcal infections during the reporting period; this will include for each case:
 - The serotype of *Neisseria meningitides*

- The type and timing of vaccination and revaccination against *Neisseria meningitides*
- The circumstances under which the patient sought/received treatment for meningococcal infection, including the patient's use of the Soliris Patient Safety Card
- The clinical course of the meningococcal infection, and the outcome of the infection
- An assessment of prescriber and patient understanding regarding the safe use of Soliris i.e., the results of surveys administered to prescribers and patients.
- Medication Guide distribution data, including the number of Medication Guides dispensed in comparison to the number of prescriptions shipped during the reporting period, a report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24, a report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- Based on the information submitted, an assessment of and conclusion regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

2. REMS ELEMENTS

2.1 Soliris Medication Guide

The Soliris Medication Guide, which is part of the package insert, is packaged with every vial of Soliris. The Medication Guide will be provided to all HCPs as initial training along with educational material. Through the enrollment process, each HCP will agree to dispense the Medication Guide to each patient. Additionally, patients will receive a copy of the Medication Guide through OneSource during enrollment. Copies of the Medication Guide will be provided by the Soliris Specialist and also be available on the internet at www.Soliris.net, and available by fax or mail through OneSource.

2.2 Elements to Assure Safe Use

2.2.1 Initial Prescriber Education

At the initial contact, any prescriber interested in treating a patient with Soliris will receive a Prescriber Introductory Letter which will provide important information on the Soliris REMS. This Introductory Letter is included in Section 4.1.

The tools used for the prescriber training include the following:

- Medication Guide: the revised Medication Guide was described in Section 2.1
- Soliris Dosing and Administration Guide: this document is specific for healthcare professionals and summarized important aspect of the delivery of Soliris.
- Soliris Patient Safety Card: all patients must receive a safety card which they must have at all time. The healthcare professionals will provide the safety card to each patient and will use it as an education material.
- Patient safety brochure, *Important Safety Information about Soliris*.
- Prescriber safety brochure, *Important Safety Information about Soliris*.

2.2.2 Prescriber Enrollment

Physicians ordering Soliris will be contacted by OneSource personnel or field representatives (RAMs) and informed that the prescribing physician must agree to enroll in the REMS program as a condition of the drug being shipped. All physicians who are interested in Soliris for potential patients will be allowed to enroll in the REMS program.

OneSource personnel or field representatives will contact the office and provide a number of methods to complete physician enrollment:

1. Enrollment forms may be faxed to the office and returned to Alexion once completed,
2. Enrollment forms may be mailed to the office and returned to Alexion once completed,
3. The OneSource or field personnel can read the physician enrollment form over the phone to the prescribing physician, acquire enrollment from the prescribing physician over the phone and then record the agreement electronically. After recording the enrollment over

the phone, the forms and acknowledgement of enrollment will be mailed or faxed to the physician's office.

4. Field representatives may visit the office and deliver and collect the enrollment form or acknowledge the form electronically.
5. The physician may acknowledge the REMS enrollment form by accessing the form through the Soliris.net website.

In addition, Alexion has revised the Physician Enrollment Form. The form will now be in the Business Reply Card Format where physicians can mail the form back to Alexion in a self-addressed postage paid envelope.

2.2.3 Prescriber Reminder Education

Soliris Specialists will contact all prescribers once a year to remind them of the OneSource Safety Support program and will emphasize the need for the safe use of Soliris. Soliris Specialists will further review and discuss the educational material previously provided and will update them on any new data available to Alexion.

2.2.4 Patient Education and Voluntary Enrollment

Patients (or Caregivers, or Legal Guardians) of a pediatric patient considering Soliris treatment will be given a copy of the educational material by the health care provider. The HCP will review the content of the materials with the patient. Patient will also have the opportunity to review and discuss the educational material with an Alexion Nurse Case Manager. The patient will have the opportunity to ask any questions that they may have. The Alexion Nurse Case Manager at OneSource will provide further assistance in returning the Enrollment Form for patients who choose to enroll. A copy of the Patient Introductory Letter and Voluntary Enrollment Form is available in Section 4.2.

3. OTHER RELEVANT INFORMATION

3.1 Soliris Safety Observation Program

Each patient treated with Soliris is subject to certain monitoring

3.2 Survey

Alexion will conduct annual surveys of HCPs and patients to assess patient and HCP understanding of the REMS materials which communicate important safety information associated with Soliris treatment and steps that can be taken to minimize those risks. Participants will be asked to indicate which educational materials have been read or referenced over the survey period and how recently the survey participant consulted these materials over the past year.

Patient Survey

The patient survey will ask a series of questions to gauge the Patient's (or Caregiver's, or Legal Guardian's) understanding of the key REMS concepts, including and not limited to:

- Risk of meningococcal infection
- Need for meningococcal vaccinations and revaccinations
- Use of Soliris Patient Safety Card
- Warning sign of infection
- What to do in the event of infection, i.e., use of Patient Safety Card

HCP Survey

The HCP survey will ask a series of questions to gauge the physician's understanding of the key REMS concepts, including and not limited to:

- Risk of meningococcal infection
- Need for meningococcal vaccinations and revaccinations
- Need to educate patients regarding the use of the Soliris Patient Safety Card
- Need for continuous reinforcement of the risks associated with Soliris treatment

Through these analyses, Alexion will also gather feedback from HCPs on the utility in clinical practice of the tools and materials contained in the OneSource Safety Support Program. The feedback received will be utilized in assessing and improving the effectiveness of the REMS as needed.

3.3 Other Important Safety Information

Alexion Global Pharmacovigilance will write a narrative summary and analysis of the following adverse events during the reporting period including:

- Serious Infusion reactions
- Thrombotic events
- Pregnancy
- Malignancy
- Death

4. DOCUMENTS LISTED IN THE ONESOURCE SAFETY SUPPORT PROGRAM

4.1 Prescriber Introductory Letter and Enrollment Form

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

Before prescribing Soliris, consider these important safety concerns:

- *Neisseria meningitidis* is a known risk with Soliris treatment and prevention of *Neisseria meningitidis* through the use of immunization with a meningococcal vaccine two weeks prior to receiving Soliris is required.
- Patients treated with Soliris who have received a meningococcal vaccine are still at risk for meningococcal infections, including meningitis or meningococcal sepsis.
- Administer meningococcal vaccine according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations for the duration of Soliris therapy.

The boxed warning included in the prescribing information is as follows:

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early (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 a meningococcal vaccine 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 *Serious Meningococcal Infections* (5.1) for additional guidance on the management of the risk of meningococcal infection.)**
- **Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program (5.2). Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747).

SEE FULL PRESCRIBING INFORMATION FOR COMPLETE BOXED WARNING INCLUDING WARNING, PRECAUTIONS, AND ADVERSE REACTIONS

Refer to the full Prescribing Information for complete safety information.

The OneSource Program is purposed to increase awareness of the risks of meningococcal infection.

To get started in the Program, you must complete and submit the enclosed Prescriber Enrollment Form electronically or fax it to Soliris OneSource Safety Support Program at 1-877-580-2596 (ALXN), or contact Alexion by phone at 1-888-765-4747 to enroll. Once enrolled, your Soliris Specialist will provide you with an educational kit that contains resources to help you understand the OneSource Program.

The educational kit will include:

- Prescriber Introductory Letter and Enrollment Form (See Section 4.1)
- Dosing and Administration Guide (See Section 4.10)
- Soliris Medication Guide (See Section 4.6)
- Soliris Patient Safety Card (See Section 4.7)
- Patient Introductory Letter and Voluntary Enrollment Form (See Section 4.2)
- Soliris Safety Observation Program (See Section 4.3)

Additional kits are available through your Soliris Regional Account Manager, the Soliris.net website, or OneSource (1-888-765-4747).

Adverse Event Reporting

Report adverse drug reactions to Alexion Pharmaceuticals, Inc. at 1-888-SOLIRIS (1-888-765-4747). Alternatively, this information may be reported to the FDA MedWatch Reporting System by phone at 1-800-FDA-1088 (1-800-332-1088) or by mail using Form 3500 at www.fda.gov/medwatch.

Please see the enclosed complete Prescribing Information.

If you have any questions please notify your Regional Account Manager (RAM), OneSource (1-888-765-4747), or visit the Soliris.net website.

We are happy to be of assistance to you,

The OneSource Team

ONESOURCE SAFETY SUPPORT PROGRAM HEALTHCARE PROVIDER ENROLLMENT FORM

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

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

I agree to:

- review the product labeling and educational materials and comply with the safety instructions for use, including ensuring meningococcal vaccination status
- counsel Patients (or Caregivers, or Legal Guardians) and provide the patient educational materials to the patient (or Caregivers, or Legal Guardians) including the Soliris Patient Safety Card, and the Soliris Medication Guide
- ensure that the Patients (or Caregivers, or Legal Guardians) receives the Medication Guide
- intend to promptly report cases of meningococcal infection, including the patient's clinical outcomes, by contacting OneSource Safety Support Program (Alexion Pharmaceuticals, Inc.) at 1-888 SOLIRIS (1-888-765-4747) or reporting the information to FDA MedWatch Reporting System by phone at 1-800-FDA-1088 (1-800-332-1088) or by mail using Form 3500 at www.fda.gov/medwatch
- revaccinate patients in accordance with Advisory Committee on Immunization Practices (ACIP) recommendations for the duration of Soliris therapy

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early (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 a meningococcal vaccine 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 *Serious Meningococcal Infections* (5.1) for additional guidance on the management of the risk of meningococcal infection.)**

- **Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program (5.2). Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747).

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

Name (printed)

Signature

Date

Title

Specialty: _____

Office

Name: _____

Address: _____

City: _____

Phone

Number: _____

Second Office

Name: _____

Address: _____

City: _____

Phone Number: _____

E-mail: _____

State: _____

Country: _____

Fax Number: _____

E-mail: _____

State: _____

Country: _____

Fax Number: _____

To register please complete this form in its entirety and fax to Alexion at 1-877-580-2596 (ALXN) or return by e-mail at OSSP@alxn.com or by mail at:

Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
Attn: OneSource Safety Support Program

4.2 Patient Introductory Letter and Voluntary Enrollment Form

OneSource Safety Support Program

The OneSource™ Safety Support Program has been developed by Alexion Pharmaceuticals, Inc., to provide educational information and safety monitoring for people being treated with Soliris® (eculizumab).

The OneSource Safety Support Program is designed to inform you about the risks and benefits of Soliris. As part of the OneSource Safety Support Program, you will receive the following materials. For your convenience, these materials are enclosed. These materials will be reviewed with you by your healthcare provider.

- Medication Guide – The Medication Guide describes important safety information associated with the use of Soliris.
- Patient Safety Card – The Patient Safety Card contains safety guidance for Soliris patients and their healthcare providers. Your physician should discuss the importance and the proper use of this card with you. We strongly recommend that every Soliris patient carry this card at all times to show to any healthcare professional involved in their care.

If you have any questions about this information, be sure to discuss them with your doctor.

We are happy to be of assistance to you,

The OneSource Team

1-888-SOLIRIS

ONESOURCE SAFETY SUPPORT PROGRAM

VOLUNTARY PATIENT ENROLLMENT FORM

Please carefully read this Soliris (eculizumab) OneSource Safety Support Patient Enrollment Form before you begin treatment with Soliris. Do not hesitate to ask your healthcare provider any questions regarding the information provided below. Your healthcare provider will review important safety information regarding Soliris treatment, and answer any questions you have about your treatment.

Patients should seek medical attention immediately if they develop headache with nausea and/or vomiting or headache and fever, even if they do not have their Soliris Patient Card with them.

Important safety information you should know about Soliris.

- Soliris treatment lowers the ability of your immune system to fight infections.
- Soliris increases your chance of getting serious and life-threatening meningococcal infections.
 - As a safety precaution, patients should be vaccinated against meningococcal infection before starting Soliris.
 - Your healthcare provider will make sure you receive this vaccine at least 2 weeks before your first infusion, unless you have already had this vaccine, or your doctor decides that urgent treatment with Soliris is needed.
 - A meningococcal vaccine does not prevent all meningococcal infections. Your doctor will provide you with the tools and information you will need to identify and take early action if you suspect that you have a meningococcal infection.
- If you had a meningococcal vaccine in the past, you might need a booster dose before starting Soliris. Your doctor will decide if you need another dose of a meningococcal vaccine.

Program Materials

Your healthcare provider will provide a copy of the Medication Guide prior to you starting your treatment with Soliris. Please review this information. If you have any questions, speak with your health care provider.

Additionally, you will receive a Soliris Patient Safety Information card that you should **carry on you at all times. Show this card to any doctor involved in your treatment.** This card lists the following symptoms of infection that, if experienced, **requires you to contact your doctor immediately:**

- headache with nausea or vomiting
- headache with fever

- headache with a stiff neck or stiff back
- fever of 103° F or 39.4° C or higher
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

If you cannot reach your doctor, go to an emergency room and immediately show them your Soliris Patient Safety Information Card.

Who should not receive Soliris?

Do not receive Soliris if you

- Have a meningococcal infection
- Have not been vaccinated with or are not up to date with a meningococcal vaccine.

Tell your doctor if you:

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

How do I take Soliris?

Soliris is given through a vein (I.V. infusion) over 35 minutes.

What are the possible side effects of Soliris?

Soliris increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections may be fatal if not recognized and treated early.

Common side effects with Soliris include:

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

Call your doctor if you have any of these side effects. These are not all the side effects with Soliris. Ask your doctor for more information.

For More Information about Soliris

You can find additional information by calling Soliris OneSource Safety Support at 1-888-SOLIRIS (1-888-765-4747) or through the Soliris.net website.

Patient or Caregiver or Legal Guardian Signature for Treatment with Soliris

- I have read this Patient Information Form.
- I have had the opportunity to ask my healthcare provider questions regarding important safety information regarding Soliris treatment. I understand the explanations provided.
- I understand that I must fulfill my requirements regarding vaccination and revaccination.

My signature indicates that I have read, understood, and agree with all the statements above.

SIGNATURES

Patient or Caregiver or Legal Guardian (printed)

Patient or Caregiver or Legal Guardian (signature)

Date

Please fax to Alexion at 1-877-580-2596 (ALXN) or return by e-mail at OSSP@alxn.com or by mail to:

Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
Attn: OneSource Safety Support Program

4.3 Soliris Safety Observation Program

4.3.1 Synopsis

Patients treated with Soliris will be included in the Soliris Safety Observation Program to collect information regarding their demographics, baseline status, treatment, and selected safety data including predefined serious adverse events of meningococcal infection, serious infections defined as those infections resulting in hospitalization or death, possible hemolysis in PNH patients after discontinuation of Soliris, or severe TMA complications in aHUS patients after discontinuation of Soliris. Serious infusions reactions, thrombotic events, pregnancy, malignancy, and death will also be collected.

The objective is to gather, maintain, assess, and report safety data including solicited predefined serious adverse events (SAEs) and selected adverse events associated with the use of Soliris.

In addition, the Soliris Safety Observation Program will encourage the usual spontaneous adverse event reporting apart from the solicited predefined events.

Primary objective:

- To calculate the incidence of predefined adverse events associated with risks of Soliris that resulted in a serious outcome in patients receiving Soliris.

Secondary objectives:

- To determine the frequency of Soliris discontinuation and the outcome in patients who discontinue Soliris
- To assess the frequency of meningococcal vaccination
- To assess the frequency of other vaccinations
- To assess the frequency of appropriate antibiotic prophylaxis

Key elements of the Soliris Safety Observation Program include:

- Patients from the OneSource Safety Support Program are enrolled in the Soliris Safety Observation Program
- All available patient baseline demographic data will be captured and entered into the Soliris Safety Observation Program
- Healthcare Professionals (HCPs) will be encouraged to report adverse events in real time by contacting the OneSource Safety Support Program. All reported SAEs will be followed up by Alexion Global Pharmacovigilance for completeness and outcome
- At 6-month intervals, using the Soliris Safety Questionnaire, the Soliris Specialist will ask the enrolled patient or patient's Caregiver or Legal Guardian and patient's HCP if any predefined adverse events associated with Soliris risks were experienced by the patient receiving Soliris therapy
- The predefined risks of possible serious hemolysis in PNH patients or severe TMA complications in aHUS patients following discontinuation of Soliris treatment will be captured in the Soliris Discontinuation/Post Discontinuation form.

- The Soliris Specialist will ask the enrolled Patient, patient's Caregiver or Legal Guardian and patient's HCP if any other not predefined SAE was experienced and whether it was previously reported to the OneSource Safety Support Program or the Alexion Medical Information Department. If the event was not previously reported, the Soliris Specialist will facilitate the intake of the SAE and report it to Global Pharmacovigilance or designee as per established procedures.
- If a predefined SAE or pre-specified safety data was observed or experienced, the Soliris Specialist will ask if it has been reported to One Source Safety Support Program or the Alexion Medical Information Department. If the SAE or pre-specified safety data was not previously reported, the Soliris Specialist will facilitate the intake and report it to Global Pharmacovigilance or designee as per established procedures.

The aggregate data collected in the Soliris Safety Observation Program will be reviewed and reported every six months for one year, then annually thereafter.

Soliris Safety Observation Program Design

The Soliris Safety Observation Program is a descriptive follow-up study of patients who have received Soliris in the United States. Soliris-treated patients will be enrolled and followed-up in the Soliris Safety Observation Program through their prescribing HCPs.

Collection of Baseline Patient Demographic Information

Patients will be entered into the Soliris Safety Observation Program by the submission of basic demographic information (name, date of birth, and gender) using the Patient Baseline Data Form. The enrolled Patient, or patient's Caregiver or Legal Guardian and HCP will be requested to provide all additional available baseline data at the time of enrollment or within 30 days of patient enrollment using the Patient Baseline Data Form. The data will be collected for each patient to the extent the information is available.

The data will serve as a basis for comprehensive assessment of the predefined SAEs and safety data as well as for analysis. These data will be utilized as aggregate data in Soliris safety analyses.

See Soliris Patient Baseline Data Form

Collection of Adverse Events

Enrolled HCPs will be educated on the purpose and objectives of the Soliris Safety Observation Program. They will also be educated on the risks associated with Soliris treatment and instructed to report adverse events to the OneSource Safety Support Program. HCPs will be encouraged to report adverse events in real time. All reported predefined and not predefined SAEs and events of interest will be followed up by Alexion for completeness and outcome. All meningococcal infections will be reported to the agency in an expedited manner in 15-day reports. Other events of interest will be reported as required.

In addition, the enrolled HCP will be prompted and reminded every 6 months to complete the Serious Adverse Events/Events of Interest Questionnaire. The 6-month review cycle will be HCP-based and determined at the time of HCP enrollment; all newly enrolled patients will be

entered into their respective HCP's 6-month review cycle. The purpose of these communications is to 1) remind the enrolled HCP of the importance of reporting adverse events observed in patients receiving Soliris, 2) ask if the enrolled HCP observed and reported any SAEs in their patients receiving Soliris, and 3) facilitate the intake of any non-reported SAEs.

See Soliris Serious Adverse Events/Events of Interest Questionnaire

Reported cases of SAEs will be followed by Alexion using the processes established for intake of serious adverse event reporting. The Alexion safety database will be the repository of all AE reports received.

SAE reports will be sent to the Regulatory Agency in an expedited manner per local regulatory requirements.

Patients enrolled in the OneSource Safety Support Program who experience an AE will be able to report the AE directly to the OneSource Safety Support Program. These AEs will be triaged in the OneSource Safety Support Program and entered in the Alexion safety database.

All serious, medically confirmed AEs will be reported in the periodic report to the FDA. All reported adverse events included in the Soliris Safety Observation Program will be searchable in the Alexion safety database for analysis as needed, by event or by patient.

Re-assessment of the risks will be based on drug experience which is dependent upon frequency of events and patient enrollment into the program.

Patients Lost to Follow-up and Patients who Discontinue Soliris

If during the 6-month Soliris Safety Questionnaire call, a patient is reported by the HCP as 'lost to follow up', the Soliris Specialist will attempt to contact the patient. If the patient is reached and has switched to a different HCP, the Soliris Specialist will check against the HCP database and verify if the current HCP is enrolled in the program. If the patient indicates that treatment has been discontinued, the Soliris Specialist will obtain the last date of Soliris treatment as well as information provided by the HCP related to follow-up after Soliris discontinuation, including whether serious hemolysis (PNH patients) or severe TMA complications (aHUS patients) has been observed. In addition, after receiving a report by the HCP that a patient is "lost to follow-up," a Soliris Specialist will attempt to contact the patient. Where appropriate, names of individuals who cannot be reached and continue to be lost to follow up will be provided to the National Death Index (NDI) of the National Center for Health Statistics (NCHS).

See Soliris Discontinuation/Post Discontinuation Form

4.4 Observation Data Reporting Forms

4.4.1 Soliris Baseline Data Form

Soliris Baseline Data Form

Patient Information		
Initials:	Date of Birth (mm-dd-yyyy):	
Patient Identification Number:	Gender: ☐ Male ☐ Female	Race:
Indication for Soliris: ☐ PNH ☐ aHUS ☐ Other,		
Date of diagnosis (mm-dd-yyyy):		
Concurrent Medical Conditions (Check all that apply)		
☐	Acute Myelogenous Leukemia, date (mm-dd-yyyy):	
☐	Aplastic Anemia, date (mm-dd-yy):	
☐	Myelodysplastic Syndrome, date (mm-dd-yyyy):	
☐	Myeloproliferative Disorder, date (mm-dd-yyyy):	
	Specify:	
☐	Renal disease date (mm-dd-yyyy):	
☐	Transplant, specify: Date (mm-dd-yyyy):	
☐	Thromboembolic events, specify:	
☐	Other, specify:	
Other pertinent medical history (specify):		
Other hematological disorders	☐ No	Date (mm-dd-yyyy):
	☐ Yes, specify:	
Current Adjunct Therapy		
Anticoagulation/Antithrombotic	☐ No	☐ Yes, specify:
Erythropoietin	☐ No	☐ Yes, specify:
Steroids	☐ No	☐ Yes, specify:
Immunosuppressant Therapy	☐ No	☐ Yes, specify:
Analgesic use	☐ No	☐ Yes, specify:
Plasma therapy	☐ No	☐ Yes, frequency:
Plasma intervention	☐ No	☐ Yes, frequency:
Dialysis	☐ No	☐ Yes, specify:
☐ Meningococcal vaccine, date (mm-dd-yyyy):	Vaccine name/type:	
☐ Hemophilus vaccine, date (mm-dd-yyyy):		
☐ Pneumococcal vaccine, date (mm-dd-yyyy):		
☐ Antibiotic prophylaxis, specify:	Date (mm-dd-yyyy):	
☐ Revaccination, specify	Date (mm-dd-yyyy):	
☐ Revaccination, specify	Date (mm-dd-yyyy):	
☐ Revaccination, specify	Date (mm-dd-yyyy):	

Soliris Start Date (mm-dd-yyyy):			
Soliris Dose:			
Reporter Information*			
	Reporter/Title (print)	Soliris Program ID#	Date of Report (mm-dd-yyyy)
Reporter: ☐ Physician ☐ Other Healthcare Professional ☐ Soliris Specialist			
Signature			
Please fax the completed form to OneSource Safety Support Program 1-877-580-2596 (ALXN) OR Return by email to: OSSP@alxn.com OR Return by mail to: Alexion Pharmaceuticals, Inc. 352 Knotter Drive Cheshire, CT 06410 Attn: OneSource Safety Support Program If you have question, please contact Soliris OneSource at 1-888-SOLIRIS (1-888-765-4747)			

*This form may be completed and signed by Physician, other Healthcare Professional, or Soliris Specialist

4.4.2 Soliris Serious Adverse Events/Events of Interest Questionnaire

Soliris Serious Adverse Events/Events of Interest Questionnaire

Patient Information			
Initials:			
Patient Identification Number:		Diagnosis:	
Date of Birth (mm-dd-yyyy):		☐ Male ☐ Female	
Soliris: Date of Last Dose (mm-dd-yyyy):		Dose:	
☐ Meningococcal vaccine, date (mm-dd-yyyy):		Vaccine name/type:	
☐ Hemophilus vaccine, date (mm-dd-yyyy):			
☐ Pneumococcal vaccine, date (mm-dd-yyyy):			
☐ Antibiotic prophylaxis, specify:		Date (mm-dd-yyyy):	
☐ Revaccination, specify		Date (mm-dd-yyyy):	
<i>Neisseria meningitidis</i> ☐ No			
☐ Yes, Onset Date (mm-dd-yyyy):			
Did patient present Soliris Patient Safety Card? ☐ Yes ☐ Unk ☐ No			
Hospitalization	☐ Unk ☐ No		Diagnosis:
	☐ Yes	Admission Date (mm-dd-yyyy):	
		Discharge Date (mm-dd-yyyy):	
Blood cultures	☐ Unk ☐ No	☐ Yes, result:	
CSF	☐ Unk ☐ No	☐ Yes, result:	
Serogroup:	☐ Unk ☐ A ☐ B ☐ C ☐ Y ☐ W135 ☐ X ☐ Other, specify:		
Antibiotic	☐ Unknown ☐ ceftriaxone ☐ cefotaxime ☐ cefuroxime		
	☐ Other, specify:		
Outcome	☐ Unknown ☐ Recovered, date (mm-dd-yyyy):		Date (mm-dd-yyyy):
	☐ Recovered with sequelae, specify:		
	☐ Death, cause of death:		Date (mm-dd-yyyy):
Serious Infection ¹	☐ No ☐ Yes, specify:		Date (mm-dd-yyyy):
Hospitalization	Admission Date (mm-dd-yyyy):	Diagnosis:	
Blood cultures	☐ Unk ☐ No	☐ Yes, result:	
Antibiotic treatment: ☐ Unk ☐ No ☐ Yes, specify:			
Outcome	☐ Unknown ☐ Recovered, Date (mm-dd-yyyy):		Date (mm-dd-yyyy):
	☐ Recovered with sequelae, specify:		
	☐ Death, specify cause:		Date (mm-dd-yyyy):
Pregnancy	No ☐		
	Yes ☐	Current status:	

	Outcome:		
Serious Infusion reaction	☐ No		
	☐ Yes, specify:		Date (mm-dd-yyyy):
Outcome:	☐ Unknown ☐ Recovered,		Date (mm-dd-yyyy):
Thrombosis	☐ No		
	☐ Yes, specify:		Date (mm-dd-yyyy):
Outcome:	☐ Unknown ☐ Recovered,		Date (mm-dd-yyyy):
Malignancy	☐ No		
	☐ Yes, specify:		Date (mm-dd-yyyy):
Outcome:	☐ Unknown ☐ Recovered,		Date (mm-dd-yyyy):
Death	☐ No		
	☐ Yes, Probable cause of death ☐ Unk or specify:		Date (mm-dd-yyyy):
Reporter Information*			
	Reporter/Title (print)	Soliris Program ID#	Date of Report (mm-dd-yyyy)
Reporter ☐ Physician ☐ Other Healthcare Professional ☐ Soliris Specialist			
Signature			
Please fax the completed form to OneSource Safety Support Program 1-877-580-2596 (ALXN) OR Return by email to: OSSP@alxn.com OR Return by mail to: Alexion Pharmaceuticals, Inc. 352 Knotter Drive Cheshire, CT 06410 Attn: OneSource Safety Support Program If you have question, please contact Soliris OneSource at 1-888-SOLIRIS (1-888-765-4747)			

¹ For serious infections that result in hospitalization or death

* This form may be completed and signed by Physician, other Healthcare Professional, or Soliris Specialist

4.4.3 Soliris Patient Discontinuation/Post-Discontinuation Form - PNH

Soliris Patient Discontinuation/Post-Discontinuation Form - PNH

Patient Information			
Initials:		Diagnosis:	Patient Identification Number:
Date of Birth (mm-dd-yyyy):		☐ Male ☐ Female	
Primary Reason for Discontinuation			
☐ Bone Marrow Transplant			
☐ Patient died/Date (mm-dd-yyyy):		Probable cause of death:	
☐ Other, specify:			
Date of last dose of Soliris (mm-dd-yyyy):			
Serious Hemolysis		☐ No	
		☐ Yes Outcome/Date (mm-dd-yyyy):	
LDH (units) at Baseline (prior to Soliris treatment)		Value:	ULN=
LDH (units) at Discontinuation		Value:	ULN=
LDH (units) at 8 weeks Post Discontinuation		Value:	ULN=
		Baseline	Specify
Was LDH at the time of the significant adverse clinical outcome exceeding the patient's baseline LDH level?		No ☐	Yes ☐
Was there a >25% absolute decrease in PNH Type RBC clone size (in the absence of dilution due to transfusion) in one week or less?		No ☐	Yes ☐
Was Hgb level <5 gm/dL or less?		No ☐	Yes ☐
Was there a decrease of >4 gm/dL in one week or less?		No ☐	Yes ☐
Was there a 50% increase in serum creatinine from baseline?		No ☐	Yes ☐
Angina		No ☐	Yes ☐
Change in mental status		No ☐	Yes ☐
Thrombosis		No ☐	Yes ☐
Was there a significant adverse clinical outcome associated with hemolysis? No ☐ Yes ☐			
Specify/Outcome/Date (mm-dd-yyyy):			
Reporter Information*			
		Reporter/Title (print)	Soliris Program ID#
			Date of Report (mm-dd-yyyy)
Reporter			
☐ Physician			
☐ Other Healthcare Professional			
☐ Soliris Specialist			
Signature			

Patient Information

Please fax the completed form to OneSource Safety Support Program 1-877-580-2596 (ALXN)

OR

Return by email to: OSSP@alxn.com

OR

Return by mail to:

Alexion Pharmaceuticals, Inc.

352 Knotter Drive

Cheshire, CT 06410

Attn: OneSource Safety Support Program

If you have question, please contact Soliris OneSource at 1-888-SOLIRIS (1-888-765-4747)

* This form may be completed and signed by Physician, Other Healthcare Professional, or Soliris Specialist.

4.4.4 Soliris Patient Discontinuation/Post-Discontinuation Form - aHUS

Soliris Patient Discontinuation/Post-Discontinuation Form - aHUS

Patient Information			
Initials:		Diagnosis:	
Date of Birth (mm-dd-yyyy):		Patient Identification Number:	
		☐ Male ☐ Female	
Primary Reason for Discontinuation			
☐ Patient died/Date (mm-dd-yyyy):		Probable cause of death:	
☐ Cause, specify:			
Date of last dose of Soliris (mm-dd-yyyy):			
Severe TMA Complications		☐ No	
		☐ Yes Outcome/Date (mm-dd-yyyy):	
Platelet (units) at Baseline (prior to Soliris treatment)		Value:	ULN=
Platelet (units) at Discontinuation		Value:	ULN=
Platelet (units) after discontinuation		Value:	ULN=
Creatinine (units) at Baseline (prior to Soliris treatment)		Value:	ULN=
Creatinine (units) at Discontinuation		Value:	ULN=
Creatinine (units) after discontinuation		Value:	ULN=
		Baseline	Specify
Was there at the time of the event need for dialysis	No ☐		Yes ☐
Was there at the time of the event other important symptoms such as dyspnea? Please specify			
	No ☐		Yes ☐
	No ☐		Yes ☐
	No ☐		Yes ☐
Angina	No ☐		Yes ☐
Seizures or change in mental status	No ☐		Yes ☐
Thrombosis	No ☐		Yes ☐
Was there a significant adverse clinical outcome associated with hemolysis? No ☐ Yes ☐			
Specify/Outcome/Date (mm-dd-yyyy):			
Reporter Information*			
	Reporter/Title (print)	Soliris Program ID#	Date of Report (mm-dd-yyyy)
Reporter			
☐ Physician			
☐ Other Healthcare Professional			
☐ Soliris Specialist			
Signature			
Please fax the completed form to OneSource Safety Support Program 1-877-580-2596 (ALXN)			

Patient Information

OR

Return by email to: OSSP@alxn.com

OR

Return by mail to:

Alexion Pharmaceuticals, Inc.

352 Knotter Drive

Cheshire, CT 06410

Attn: OneSource Safety Support Program

If you have question, please contact Soliris OneSource at 1-888-SOLIRIS (1-888-765-4747)

* This form may be completed and signed by Physician, other Healthcare Professional, or Soliris Specialist.

4.5 Surveys

4.5.1 Physician/Healthcare Provider

As part of the OneSource Safety Support Program, we would like you to participate in a very brief survey to help assess the effectiveness of the Program.

Please have the Healthcare Provider who interacts with the patient receiving therapy complete the following:

TREATING PHYSICIAN NAME: _____

HEALTHCARE PROVIDER COMPLETING SURVEY:

NAME: _____

TITLE: _____

DATE OF SURVEY: _____

I have read or referenced each of the following in the past (<i>check all that apply</i>):					
	1 M	3 M	6M	1Y	Never
Soliris Package Insert (US)	☐	☐	☐	☐	☐
Soliris Medication Guide	☐	☐	☐	☐	☐
Soliris Patient Safety Card	☐	☐	☐	☐	☐
Soliris Web Site (www.soliris.net)	☐	☐	☐	☐	☐

1.	What vaccine(s) <u>must</u> all patients receive before being treated with Soliris? Select all that apply:	a) Meningococcal vaccine b) Pneumococcal vaccine c) Hepatitis B vaccine d) I don't know
2.	If a patient for whom you prescribed Soliris is not current on their meningococcal vaccine, when do they need to receive the vaccine?	a) At least 2 weeks before the first Soliris infusion b) At least 2 weeks after the first Soliris infusion c) Before their second Soliris infusion d) I don't know
3.	Based on the label, for whom is Soliris contraindicated? Select all that apply.	a) Patients with a current meningococcal infection b) Patients with a current meningococcal vaccination c) Patients with an upper respiratory infection d) I don't know

4.	Are patients on Soliris who have received a meningococcal vaccine no longer at risk for meningococcal meningitis (or meningococcal sepsis)?	a) Yes b) No c) I don't know
5.	Revaccination should be conducted with a meningococcal vaccine according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in persons with complement deficiencies.	a) Yes b) No c) I don't know
6.	Patients on Soliris are at an increased risk for serious infections with <i>Neisseria</i> species, including meningococcal meningitis and meningococcal sepsis.	a) Yes b) No c) I don't know
7.	Do you go over the Soliris Medication Guide with your patients and make sure that you have answered their questions?	a) Yes, each and every patient b) Almost all of them c) Some of them d) None of them
8.	Initial patient counseling and education on the use of Soliris is the only requirement for the continued use of Soliris.	a) Yes b) No c) I don't know
9.	Before administering Soliris, did you educate your patient about the risk of serious hemolysis following discontinuation of Soliris?	a) Yes b) No c) I don't know
10.	Do you go over the Patient Safety Card (wallet card) with your patients?	a) Yes, each and every patient b) Almost all of them c) Some of them d) None of them
11.	Your patient should carry the Patient Safety Card at all times and inform their family members and family physician that they are receiving Soliris.	a) Yes b) No c) I don't know
12.	Do you inform your patients to check the Patient Safety Card anytime they have a fever or flu-like symptoms or any other symptoms that may indicate an infection?	a) Yes, each and every patient b) Almost all of them c) Some of them d) None of them
13.	Are you aware that Soliris has not been evaluated in pregnant patients and Soliris should be used in pregnant women only if the potential benefit justifies the potential risk?	a) Yes b) No c) I don't know

14.	Should you report pregnancy in patients treated with Soliris to the Soliris toll-free number and the PNH Registry?	a) Yes b) No c) I don't know
15.	If a patient misses a dose of Soliris, should you infuse them at your earliest opportunity rather than wait for their next scheduled infusion?	a) Yes b) No c) I don't know
16.	To whom do you report suspected Soliris adverse events?	a) Alexion Pharmaceuticals b) FDA MedWatch c) Both of the above d) None of the above
17.	Do you register your patient(s) in the PNH Registry?	a) Yes, each and every patient b) Almost all of them c) Some of them d) None of them

4.5.2 Patient Annual Survey to be administered as an interview by the patients' Alexion Case Manager

Patient Number Identifier _____

Date of Survey _____

The patient's Alexion Case Manager will ask the patient if he or she has read or referenced the following tools:

Provide an introduction that describes the tools	1 M	3 M	6M	1Y	Never
Soliris Medication Guide					
Soliris Patient Safety Card					
Soliris Web Site (www.soliris.net)					

The patient's OneSource Specialist will ask the patient the following questions and record their answers.

1.	Did your healthcare provider offer to explain to you the information in the Medication Guide?	a) Yes b) No c) I did not receive the Medication Guide
2.	Did you accept the offer from your healthcare provider to explain the information in the Medication Guide?	a) Yes b) No c) I don't know
3.	Did you understand the explanation that was given to you?	a) All b) Most c) Some d) None
4.	Did or do you have any questions about the Medication Guide or Patient Safety Card? If yes, list your question below: Question:	a) Yes b) No
5.	Did you receive the Soliris Patient Safety Card?	a) Yes b) No

		c) I don't know
6.	What vaccine <u>must</u> you receive before being treated with Soliris?	a) Meningococcal vaccine b) Pneumococcal vaccine c) Hepatitis B vaccine d) I don't know
7.	Did you receive a meningococcal vaccine 2 weeks before starting Soliris?	a) Yes, right around 2 weeks before b) No, but my meningococcal vaccine is still current c) No, but I received antibiotics d) No e) I don't know
8.	How often do you need to be re-vaccinated with a meningococcal vaccine?	a) My doctor will tell me when I'm due b) Before each infusion c) If I have symptoms of a meningococcal infection d) I don't know
9.	Should you inform your family members and Primary Care physician that you are receiving Soliris?	a) Yes b) No c) I don't know
10.	While you are taking Soliris are you at an increased risk for meningitis?	a) Yes b) No c) I don't know
11.	As a Caregiver or Legal Guardian of a patient < 18 years of age, are you aware of the recommendations for other vaccinations?	a) Yes b) No c) I don't know d) Not applicable (patient is ≥18 years old)
12.	Can you get a meningococcal infection even after you receive a meningococcal vaccination?	a) Yes b) No c) I don't know
13.	Should you tell your doctor if you have a serious infection?	a) Yes b) No

		c) I don't know
14.	Which of these are the signs and symptoms of a meningococcal infection: Select all that apply	a) Confusion b) Stiff neck, back, and muscle aches c) Fever d) Headache with nausea or vomiting e) I don't know
15.	What should you do if you think you have signs and symptom of a meningococcal infection?	a) Rest and wait to see if your symptoms get worse b) Call a friend for advice c) Call your doctor right away, or get emergency care d) I don't know
16.	Do you carry the Patient Safety Card with you at all times?	a) Yes b) No c) I don't know
17.	If you experience any change in health status you should check your Patient Safety Card and tell your doctor?	a) Yes b) No c) I don't know
18.	Should you seek immediate medical attention when you experience any symptoms described in the Patient Safety Card?	a) Yes b) No c) I don't know
19.	Should you show your Patient Safety Card to your treating physician anytime you have a fever, flu-like symptoms, or any of the other symptoms listed on the card?	a) Yes b) No c) I don't know
20.	Should you tell your doctor if you are pregnant or want to become pregnant while you are receiving treatment with Soliris?	a) Yes b) No c) I don't know d) Not applicable
21.	Should you tell your doctor if you have any allergic reaction including hives, itching, or trouble breathing during or after an infusion of Soliris?	a) Yes b) No c) I don't know

22.	What should you do if you miss or forget a Soliris infusion?	a) Just skip it this time and go back to your regular schedule b) Schedule an infusion within 2 days of your regular schedule c) I don't know

4.6 Medication Guide

MEDICATION GUIDE

Soliris® (so-leer-is)
(eculizumab)

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

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

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

- **Soliris increases your risk 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 a meningococcal vaccine at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decides that urgent treatment with Soliris is needed, you should receive a meningococcal vaccine as soon as possible.**
2. **If you had a meningococcal vaccine in the past, you might need a booster dose before starting Soliris. Your doctor will decide if you need another dose of a meningococcal vaccine.**
3. **A meningococcal vaccine does not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:**
 - **headache with nausea or vomiting**
 - **headache and a fever**
 - **headache with a stiff neck or stiff back**
 - **fever of 103° F (39.4° C) or higher**
 - **fever and a rash**
 - **confusion**
 - **muscle aches with flu-like symptoms**

- **eyes sensitive to light**

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

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

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

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

What is Soliris?

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

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). PNH affects red blood cells.
- a disease called atypical Hemolytic Uremic Syndrome (aHUS). aHUS affects the blood system, kidney, and sometimes other body organs.

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

It is important that you:

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

Who should not receive Soliris?

Do not receive Soliris if you:

- have a meningococcal infection

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

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if you:

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

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

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

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes. If you have an allergic reaction during your Soliris infusion, your doctor may decide to give Soliris more slowly or stop your infusion.
- If you are an adult, you will usually receive a Soliris infusion by your doctor:
 - weekly for five weeks, then
 - every 2 weeks
- If you are less than 18 years of age, your doctor will decide how often you will receive Soliris depending on your age and body weight.
- After each infusion, you should be monitored for one hour for allergic reactions. See “What are the possible side effects of Soliris?”
- If you forget or miss a Soliris infusion, call your doctor right away.
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**

Symptoms or problems that can happen due to red blood cell breakdown include:

- drop in the number of your red blood cells
- drop in your platelet count
- confusion
- chest pain

- kidney problems
 - blood clots
 - difficulty breathing
- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

Symptoms or problems that can happen with abnormal clotting may include:

- stroke
- confusion
- seizures
- chest pain (angina)
- difficulty breathing
- kidney problems
- swelling in arms or legs
- a drop in your platelet count

What are the possible side effects of Soliris?

Soliris can cause serious side effects, including:

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

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

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

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

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

- high blood pressure
- common cold (upper respiratory infection)
- diarrhea
- headache
- nausea and vomiting
- low red blood cell count
- low white blood cell count
- urinary tract infection

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 Soliris

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

What are the ingredients in Soliris?

Active ingredient: eculizumab

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

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

Manufactured by Alexion Pharmaceuticals, Inc. 352 Knotter Drive, Cheshire, CT 06410 USA.

Revised: 09/2011

4.7 Soliris Patient Safety Card

PATIENT SAFETY INFORMATION CARD



Important Safety Information for Patients Taking Soliris®

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

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever of 103°F (39.4°C) or higher
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light



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

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

PATIENT SAFETY INFORMATION CARD

Information for the Treating Physician



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

- Meningococcal infections may 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).

 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)

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4.8 Important Safety Information about Soliris (HCP)

Before starting your patients on Soliris®.

Important safety information for the healthcare provider

Make safety your priority

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

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

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

Patient Safety Information Card

Physicians are provided with patient safety cards to give to their patients. You should discuss the importance and the proper use of this card with every patient. We strongly recommend that every Soliris patient carry this card at all times to show to any healthcare professional involved in their care. The Patient Safety Information Card contains safety guidance for Soliris patients and their healthcare providers. Prescribers should advise patients to seek medical attention immediately if they develop headache with nausea or vomiting, or headache and fever, even if they do not have their Patient Card with them.

PATIENT SAFETY INFORMATION CARD

Information for the Treating Physician



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

- Meningococcal infections may 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).

 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)

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Soliris Safety Observation Program

The Soliris Safety Observation Program is your opportunity to contribute to the understanding of the safety of Soliris. The goal of the Soliris Safety Observation Program is to collect FDA required data on patients treated with Soliris.

For more information contact OneSource Safety Support at 1-888-765-4747.

MEDICATION GUIDE

Soliris® (so-leer-is)

(eculizumab)

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

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

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

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

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

4. **You must receive a meningococcal vaccine at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decides that urgent treatment with Soliris is needed, you should receive a meningococcal vaccine as soon as possible.**
5. **If you had a meningococcal vaccine in the past, you might need a booster dose before starting Soliris. Your doctor will decide if you need another dose of a meningococcal vaccine.**
6. **A meningococcal vaccine does not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:**
 - **headache with nausea or vomiting**
 - **headache and a fever**
 - **headache with a stiff neck or stiff back**
 - **fever of 103° F (39.4° C) or higher**
 - **fever and a rash**
 - **confusion**
 - **muscle aches with flu-like symptoms**
 - **eyes sensitive to light**

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

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

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

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

What is Soliris?

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

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). PNH affects red blood cells.
- a disease called atypical Hemolytic Uremic Syndrome (aHUS). aHUS affects the blood system, kidney, and sometimes other body organs.

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

It is important that you:

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

Who should not receive Soliris?

Do not receive Soliris if you:

- have a meningococcal infection

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

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if you:

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

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

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

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes. If you have an allergic reaction during your Soliris infusion, your doctor may decide to give Soliris more slowly or stop your infusion.
- If you are an adult, you will usually receive a Soliris infusion by your doctor:
 - weekly for five weeks, then
 - every 2 weeks
- If you are less than 18 years of age, your doctor will decide how often you will receive Soliris depending on your age and body weight.
- After each infusion, you should be monitored for one hour for allergic reactions. See "What are the possible side effects of Soliris?"
- If you forget or miss a Soliris infusion, call your doctor right away.
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**

Symptoms or problems that can happen due to red blood cell breakdown include:

- drop in the number of your red blood cells
- drop in your platelet count
- confusion
- chest pain

- kidney problems
 - blood clots
 - difficulty breathing
- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

Symptoms or problems that can happen with abnormal clotting may include:

- stroke
- confusion
- seizures
- chest pain (angina)
- difficulty breathing
- kidney problems
- swelling in arms or legs
- a drop in your platelet count

What are the possible side effects of Soliris?

Soliris can cause serious side effects, including:

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

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

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

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

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

- high blood pressure
- common cold (upper respiratory infection)
- diarrhea
- headache
- nausea and vomiting
- low red blood cell count
- low white blood cell count
- urinary tract infection

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 Soliris

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

What are the ingredients in Soliris?

Active ingredient: eculizumab

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

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

Manufactured by Alexion Pharmaceuticals, Inc. 352 Knotter Drive, Cheshire, CT 06410 USA.

Revised: 09/2011

Want to learn more about Soliris®?

- Visit www.Soliris.net
- Call 1-888-SOLIRIS (1-888-765-4747)

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early (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 a meningococcal vaccine 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 *Serious Meningococcal Infections* (5.1) for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program (5.2). Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747).

4.9 Important Safety Information about Soliris (Patients)

Important Safety Information for patients

Before you begin Soliris treatment, your physician will give you a

- Medication Guide
- Soliris Patient Safety Information Card.

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

Patient Safety Information Cards.

You will receive a Patient Safety Information Card that lists symptoms of a meningococcal infection and what to do if you have them.

Your physician should discuss with you the importance and the proper use of this card.

Carry this card at all times and show it to any healthcare professional who treats you. Seek immediate treatment for headache with nausea or vomiting, or headache and fever, even if you do not have your Patient Safety Information Card with you. You should seek medical attention immediately if you develop headache with nausea or vomiting, or headache and fever, even if you do not have your Soliris Patient Safety Information Card with you.

PATIENT SAFETY INFORMATION CARD



Important Safety Information for Patients Taking Soliris®

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

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever of 103°F (39.4°C) or higher
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light



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

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

OneSource™ Treatment Support Program

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

Questions about PNH, aHUS or Soliris? Just call OneSource at 1-888-765-4747 to speak with an Alexion Nurse Case Manager.

MEDICATION GUIDE

Soliris® (so-leer-is)
(eculizumab)

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

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

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

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

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

7. **You must receive a meningococcal vaccine at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decides that urgent treatment with Soliris is needed, you should receive a meningococcal vaccine as soon as possible.**
8. **If you had a meningococcal vaccine in the past, you might need a booster dose before starting Soliris. Your doctor will decide if you need another dose of a meningococcal vaccine.**
9. **A meningococcal vaccine does not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:**
 - **headache with nausea or vomiting**
 - **headache and a fever**
 - **headache with a stiff neck or stiff back**
 - **fever of 103° F (39.4° C) or higher**
 - **fever and a rash**
 - **confusion**
 - **muscle aches with flu-like symptoms**
 - **eyes sensitive to light**

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

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

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

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

What is Soliris?

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

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). PNH affects red blood cells.
- a disease called atypical Hemolytic Uremic Syndrome (aHUS). aHUS affects the blood system, kidney, and sometimes other body organs.

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

It is important that you:

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

Who should not receive Soliris?

Do not receive Soliris if you:

- have a meningococcal infection

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

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if you:

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

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

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

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes. If you have an allergic reaction during your Soliris infusion, your doctor may decide to give Soliris more slowly or stop your infusion.
- If you are an adult, you will usually receive a Soliris infusion by your doctor:
 - weekly for five weeks, then
 - every 2 weeks
- If you are less than 18 years of age, your doctor will decide how often you will receive Soliris depending on your age and body weight.
- After each infusion, you should be monitored for one hour for allergic reactions. See “What are the possible side effects of Soliris?”
- If you forget or miss a Soliris infusion, call your doctor right away.
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**

Symptoms or problems that can happen due to red blood cell breakdown include:

- drop in the number of your red blood cells
- drop in your platelet count
- confusion
- chest pain

- kidney problems
- blood clots
- difficulty breathing
- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

Symptoms or problems that can happen with abnormal clotting may include:

- stroke
- confusion
- seizures
- chest pain (angina)
- difficulty breathing
- kidney problems
- swelling in arms or legs
- a drop in your platelet count

What are the possible side effects of Soliris?

Soliris can cause serious side effects, including:

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

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

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

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

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

- high blood pressure
- common cold (upper respiratory infection)
- diarrhea
- headache
- nausea and vomiting
- low red blood cell count
- low white blood cell count
- urinary tract infection

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 Soliris

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

What are the ingredients in Soliris?

Active ingredient: eculizumab

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

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

Manufactured by Alexion Pharmaceuticals, Inc. 352 Knotter Drive, Cheshire, CT 06410 USA.

Revised: 09/2011

Want to learn more about Soliris®?

- Visit www.Soliris.net
- Call 1-888-SOLIRIS (1-888-765-4747)

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4.10 Dosing and Administration Guide

Soliris[®] dosing and administration quick reference

Important administration guidelines

All patients must be administered a meningococcal vaccine at least 2 weeks prior to the first dose of Soliris.¹

Soliris is a chronic therapy for a chronic disease²⁻⁴

Recommended Dosage Regimen - PNH

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.

Soliris should be administered at the recommended dosage regimen time points, or within two days of these time points. [see *Warnings and Precautions (5.5)*].

Recommended Dosage Regimen - aHUS

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

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

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

Table 1: Dosing recommendations in patients less than 18 years of age

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

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

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

Supplemental dosing of Soliris is required in the setting of concomitant support with PE/PI (plasmapheresis or plasma exchange; or fresh frozen plasma infusion) (Table 2).

Table 2: Supplemental dose of Soliris after PE/PI

Type of Intervention	Most Recent Soliris Dose	Supplemental Soliris Dose With Each PE/PI Intervention	Timing of Supplemental Soliris Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	600 mg or more	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	300 mg or more	300 mg per each unit of fresh frozen plasma	60 minutes prior to each 1 unit of fresh frozen plasma infusion

Preparation of Soliris for administration

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.

1. Withdraw the required amount of Soliris from the vial into a sterile syringe and transfer the recommended dose to an infusion bag.
2. Dilute Soliris to a final concentration of 5 mg/mL. Using the table below, find the dose of Soliris and read across to determine the corresponding volume of Soliris and the amount of diluent to add to the infusion bag.

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

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

3. Gently invert the infusion bag containing the diluted Soliris solution to ensure thorough mixing of the product and diluent.
4. Inspect visually for particulate matter and discoloration prior to administration.
5. Prior to administration, the mixture should be allowed to adjust to room temperature (18°C-25°C [64°F-77°F]). **It must not be heated in a microwave or with any other heat source other than ambient air temperature.**
6. Discard any unused portion in vial; contains no preservatives.

Administering Soliris

to patients² Soliris should only be administered as an IV infusion and must be diluted to a final concentration of 5 mg/mL prior to administration. The diluted solution is a clear, colorless liquid and should be practically free of any particles.

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

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

Important safety information

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early (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 a meningococcal vaccine 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 *Serious Meningococcal Infections* (5.1) for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program (5.2). Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747).

Indication

- 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.

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

Contraindications

Do not initiate Soliris therapy in patients:

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

Adverse reactions

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

The most frequently reported adverse reactions in aHUS single arm prospective trials ($\geq 15\%$ combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

References: 1. Hillmen P, Muus P, Duhrsen U, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria *Blood*. 2007;110:4123-4128. 2. Soliris[®] [package insert]. Cheshire, CT: Alexion Pharmaceuticals Inc; 2009 3. Data on file, Alexion Pharmaceuticals Inc. 4. Rosse WF, Hillmen P, Schreiber AD. Immune-mediated hemolytic anemia. *Hematology (Am Soc Hematol Educ Program)*. 2004:48-62. 5. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA*. 2005;293:1653-1662.

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**To enroll in the Soliris REMS and order Soliris,
please call 1-888-SOLIRIS (1-888-765-4747)**

APPENDICES

The following documents are appended:

- (1) Soliris Patient Safety Card
- (2) Prescriber Introductory Letter and Enrollment Form
- (3) Patient Safety Brochure, *Important Safety Information about Soliris*
- (4) Prescriber Safety Brochure, *Important Safety Information about Soliris*
- (5) Dosing and Administration Guide
- (6) REMS website (screenshots)

Appendix 1
Soliris Patient Safety Card

PATIENT SAFETY INFORMATION CARD



Important Safety Information for Patients Taking Soliris®

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

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever of 103°F (39.4°C) or higher
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light



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

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

PATIENT SAFETY INFORMATION CARD

+ Information for the Treating Physician



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

- Meningococcal infections may 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).

+ 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 _____



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Appendix 2
Prescriber Introductory Letter and Enrollment Form

Dear Soliris® (eculizumab) Prescriber,

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

To get started in the Program, please complete the Prescriber Enrollment Form on the reverse side and either drop it in the mail; fax it to the Soliris OneSource Safety Support Program at 1.877.580.2596 (ALXN); or scan and e-mail it to OSSP@alxn.com.

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

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

I agree to:

- Review the product labeling and educational materials, and comply with the safety instructions for use, including ensuring meningococcal vaccination status
- Counsel patients (or caregivers, or legal guardians) and provide educational materials to the patient (or caregivers, or legal guardians), including the Soliris Patient Safety Information Card, and the Soliris Medication Guide
- Intend to promptly report cases of meningococcal infection, including the patient's clinical outcomes, by contacting the OneSource Safety Support Program (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 www.fda.gov/medwatch
- Revaccinate patients in accordance with the Advisory Committee on Immunization Practices (ACIP) recommendations for the duration of Soliris therapy

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected

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

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

INDICATIONS AND USAGE

Soliris is a complement inhibitor indicated for:

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

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

CONTRAINDICATIONS

Soliris is contraindicated in:

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥15% combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

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

Name (printed): _____

Signature: _____ Date: _____

Title: _____

Office Address: _____ E-mail: _____

City: _____ State: _____ ZIP: _____ Country: _____

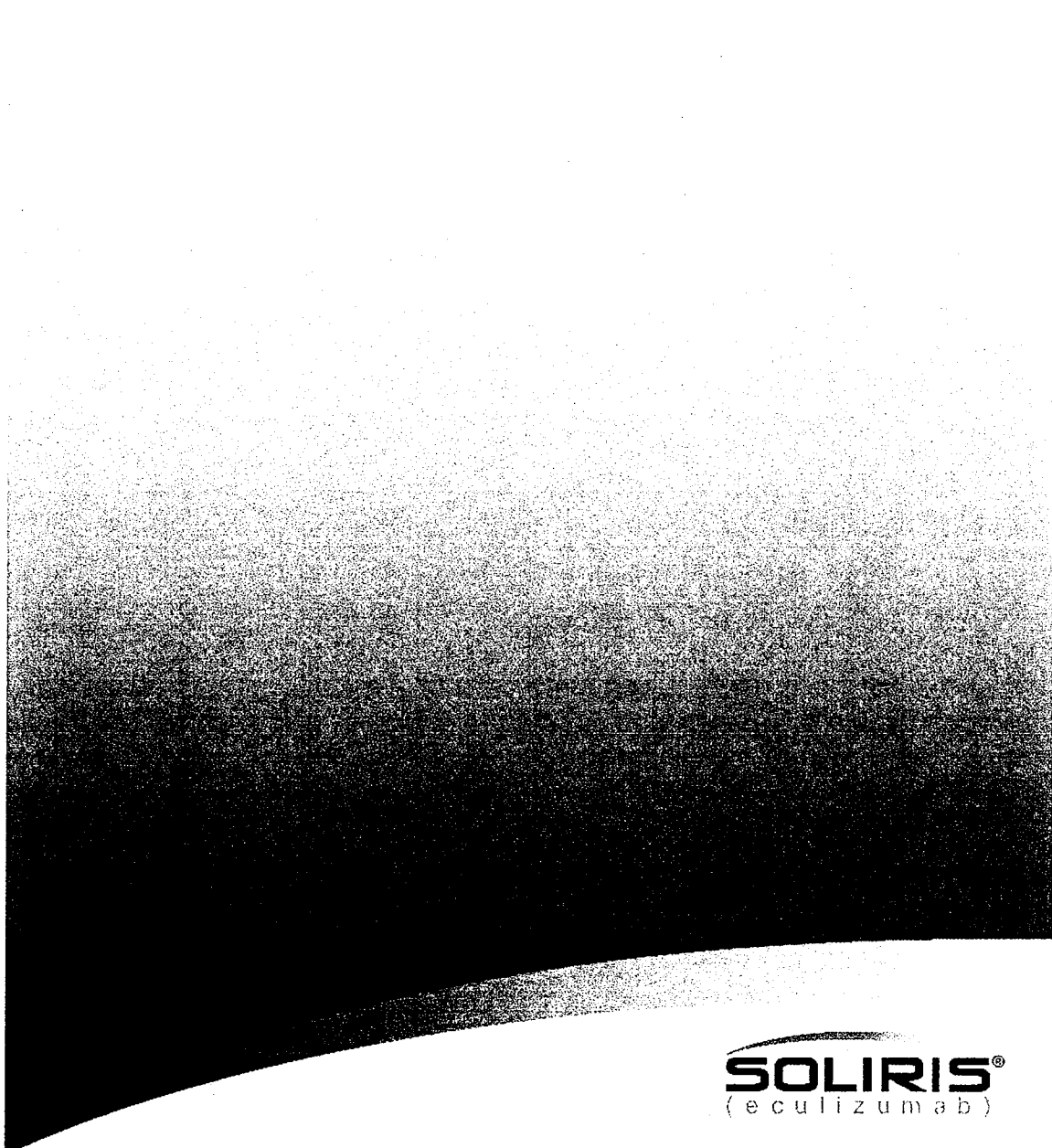
Phone Number: _____ Fax Number: _____

Appendix 3

Patient Safety Brochure, *Important Safety Information about Soliris*

Before starting on Soliris®.

Important safety information for patients



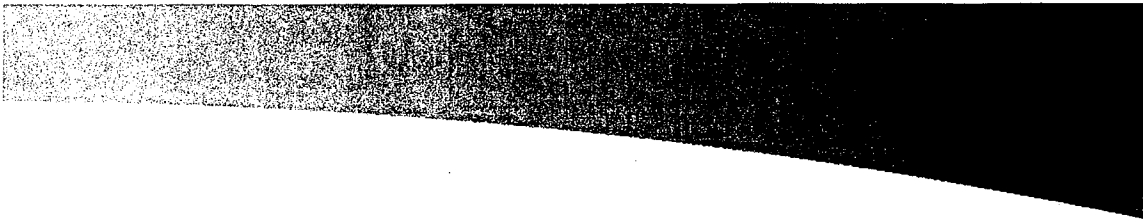
SOLIRIS[®]
(e c u l i z u m a b)



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

- ♦ Medication Guide
- ♦ Soliris Patient Safety Information Card

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



Patient Safety Information Card

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

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

PATIENT SAFETY INFORMATION CARD

+ Important Safety Information for Patients Taking Soliris®

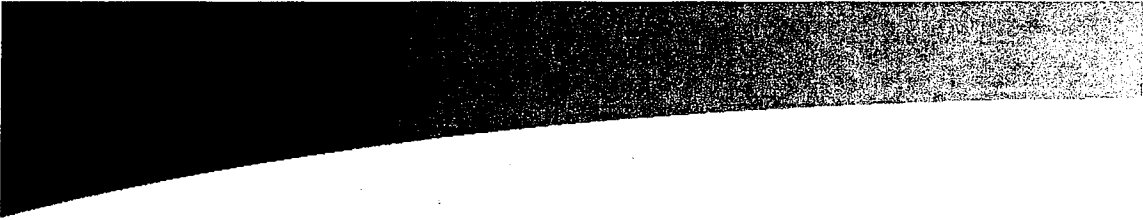
Soliris can lower the ability of your immune system to fight infections, especially meningococcal infection, which requires immediate medical attention. If you experience any of the following symptoms, you should immediately call your doctor or seek emergency medical care, preferably in a major emergency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

Soliris OneSource™ Treatment Support Program

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

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





For Discussion With Patients— Important Safety Information

MEDICATION GUIDE

Soliris® (so-leer-is) (eculizumab)

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

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

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

- Soliris increases your risk 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 a meningococcal vaccine at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decides that urgent treatment with Soliris is needed, you should receive a meningococcal vaccine as soon as possible.
2. If you had a meningococcal vaccine in the past, you might need a booster dose before starting Soliris. Your doctor will decide if you need another dose of a meningococcal vaccine.
3. A meningococcal vaccine does not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:

— headache with nausea or vomiting	— fever and a rash
— headache and a fever	— confusion
— headache with a stiff neck or stiff back	— muscle aches with flu-like symptoms
— fever of 103°F (39.4°C) or higher	— eyes sensitive to light

Please see back cover for Important Safety Information.
Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.



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

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

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

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

What is Soliris?

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

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). PNH affects red blood cells.
- a disease called atypical Hemolytic Uremic Syndrome (aHUS). aHUS affects the blood system, kidney, and sometimes other body organs.

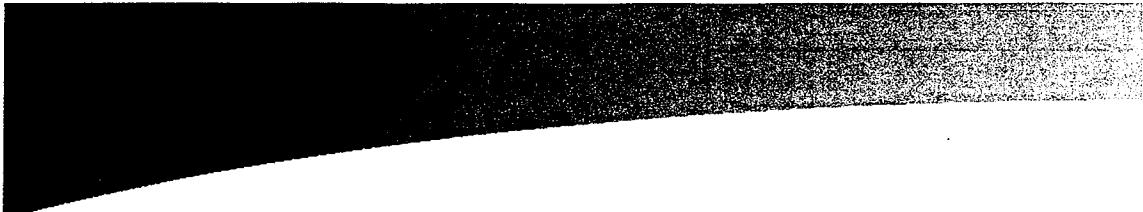
Soliris works by blocking part of your immune system. This can help your symptoms but it can also increase your chance for infection.

It is important that you:

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

**SOLIRIS**[®]
(e c u l i z u m a b)

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For Discussion With Patients— Important Safety Information (continued)

Who should not receive Soliris®?

Do not receive Soliris if you:

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

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if you:

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

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

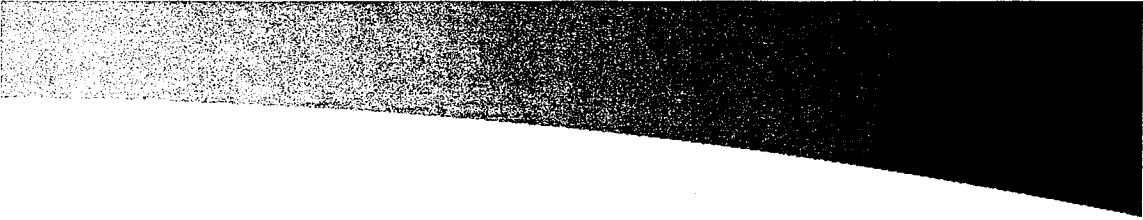
Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes. If you have an allergic reaction during your Soliris infusion, your doctor may decide to give Soliris more slowly or stop your infusion.
- If you are an adult, you will usually receive a Soliris infusion by your doctor:
 - weekly for five weeks, then
 - every 2 weeks
- If you are less than 18 years of age, your doctor will decide how often you will receive Soliris depending on your age and body weight.
- After each infusion, you should be monitored for one hour for allergic reactions. See “What are the possible side effects of Soliris?”
- If you forget or miss a Soliris infusion, call your doctor right away.

Please see back cover for Important Safety Information.

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

- 
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris®. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**

Symptoms or problems that can happen due to red blood cell breakdown include:

- drop in the number of your red blood cells
- drop in your platelet count
- confusion
- chest pain
- kidney problems
- blood clots
- difficulty breathing

- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

Symptoms or problems that can happen with abnormal clotting may include:

- stroke
- confusion
- seizures
- chest pain (angina)
- difficulty breathing
- kidney problems
- swelling in arms or legs
- a drop in your platelet count

What are the possible side effects of Soliris?

Soliris can cause serious side effects, including:

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

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

SOLIRIS®
(e c u l i z u m a b)

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For Discussion With Patients— Important Safety Information (continued)

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

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

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

- high blood pressure
- common cold (upper respiratory infection)
- diarrhea
- headache
- nausea and vomiting
- low red blood cell count
- low white blood cell count
- urinary tract infection

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 Soliris®

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

What are the ingredients in Soliris?

Active ingredient: eculizumab

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

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

Manufactured by Alexion Pharmaceuticals, Inc.
352 Knotter Drive, Cheshire, CT 06410 USA.

Revised: 09/2011

SOLIRIS®
(e c u l i z u m a b)

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Want to learn more about Soliris®?

- Visit www.Soliris.net
- Call 1.888.SOLIRIS (1.888.765.4747)

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected

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

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

The most frequently reported adverse reactions in aHUS single arm prospective trials ($\geq 15\%$ combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

ALEXION

SOLIRIS®
Eculizumab

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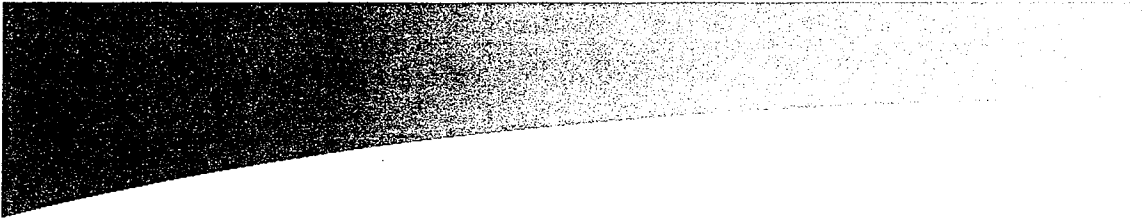
Appendix 4

Prescriber Safety Brochure, *Important Safety Information about Soliris*

Before starting your patients on Soliris®.

Important safety information for the healthcare provider

SOLIRIS®
(eculizumab)



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

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

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

2

Please see back cover for Important Safety Information.
Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.

Patient Safety Information Card

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

Prescribers should advise patients to seek medical attention immediately if they develop headache with nausea or vomiting, or headache and fever, even if they don't have their Patient Safety Information Card with them.

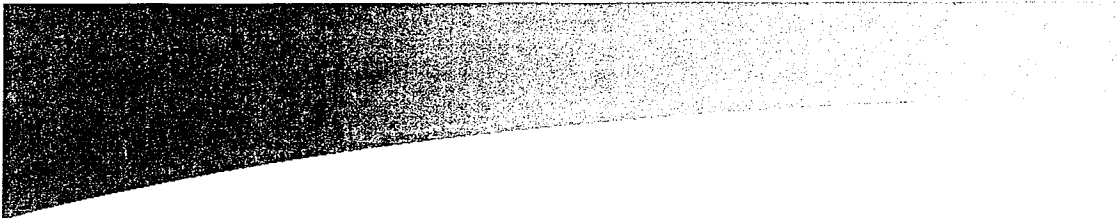
PATIENT SAFETY INFORMATION CARD



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

SOLIRIS[®]
[eculizumab]

3



For Discussion With Patients— Important Safety Information

MEDICATION GUIDE

Soliris® (so-leer-is) (eculizumab)

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

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

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

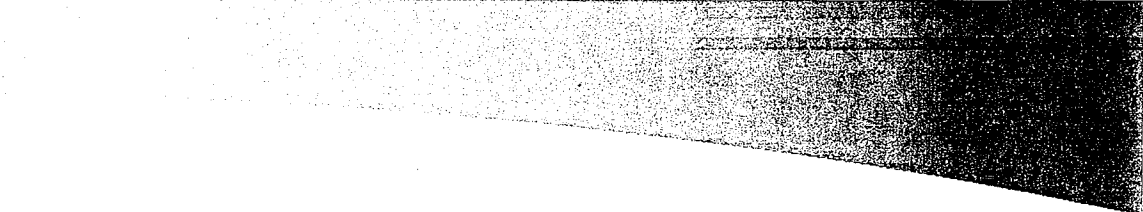
- Soliris increases your risk of getting serious and life-threatening meningococcal infections.

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

1. You must receive a meningococcal vaccine at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decides that urgent treatment with Soliris is needed, you should receive a meningococcal vaccine as soon as possible.
2. If you had a meningococcal vaccine in the past, you might need a booster dose before starting Soliris. Your doctor will decide if you need another dose of a meningococcal vaccine.
3. A meningococcal vaccine does not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:

— headache with nausea or vomiting	— fever and a rash
— headache and a fever	— confusion
— headache with a stiff neck or stiff back	— muscle aches with flu-like symptoms
— fever of 103°F (39.4°C) or higher	— eyes sensitive to light

Please see back cover for Important Safety Information.
Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.



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

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

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

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

What is Soliris?

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

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). PNH affects red blood cells.
- a disease called atypical Hemolytic Uremic Syndrome (aHUS). aHUS affects the blood system, kidney, and sometimes other body organs.

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

It is important that you:

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

**SOLIRIS**[®]
(eculizumab)

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For Discussion With Patients— Important Safety Information (continued)

Who should not receive Soliris®?

Do not receive Soliris if you:

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

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if you:

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

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

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

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes. 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?”

Please see back cover for Important Safety Information.
Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.

- If you forget or miss a Soliris® infusion, call your doctor right away.
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**

Symptoms or problems that can happen due to red blood cell breakdown include:

- drop in the number of your red blood cells
- drop in your platelet count
- confusion
- chest pain
- kidney problems
- blood clots
- difficulty breathing

- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

Symptoms or problems that can happen with abnormal clotting may include:

- stroke
- confusion
- seizures
- chest pain (angina)
- difficulty breathing
- kidney problems
- swelling in arms or legs
- a drop in your platelet count

What are the possible side effects of Soliris?

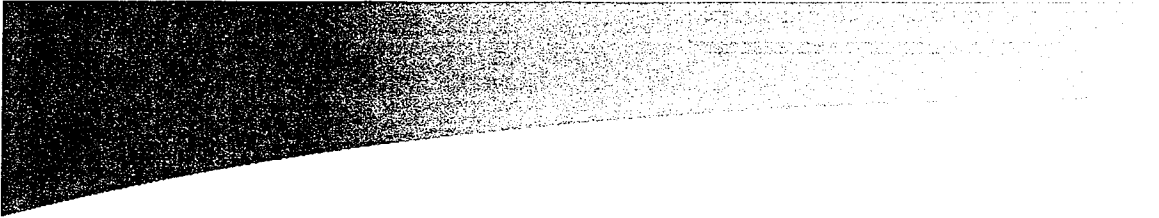
Soliris can cause serious side effects, including:

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

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

SOLIRIS®
(eculizumab)

7



For Discussion With Patients— Important Safety Information (continued)

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

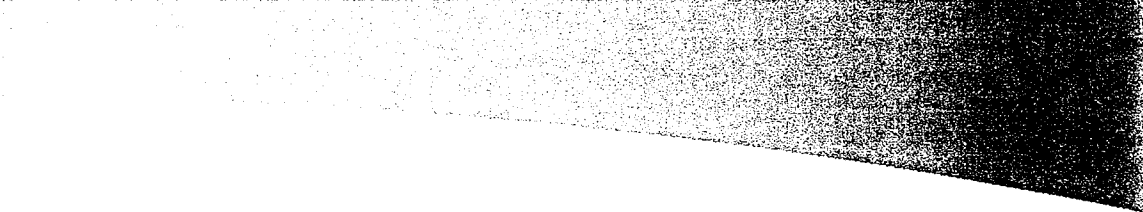
- headaches
- runny nose and colds
- sore throat
- back pain
- nausea

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

- high blood pressure
- common cold (upper respiratory infection)
- diarrhea
- headache
- nausea and vomiting
- low red blood cell count
- low white blood cell count
- urinary tract infection

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 Soliris®

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

What are the ingredients in Soliris?

Active ingredient: eculizumab

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

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

Manufactured by Alexion Pharmaceuticals, Inc.
352 Knotter Drive, Cheshire, CT 06410 USA.

Revised: 09/2011

**SOLIRIS®**
eculizumab

Want to learn more about Soliris®?

- Visit www.Soliris.net
- Call 1.888.SOLIRIS (1.888.765.4747)

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected

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

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

The most frequently reported adverse reactions in aHUS single arm prospective trials ($\geq 15\%$ combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

ALEXION

SOLIRIS®
ecorixa (c5 inhibitor)

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Appendix 5
Dosing and Administration Guide

SOLIRIS[®]
(eculizumab)

PNH | aHUS

For Paroxysmal Nocturnal Hemoglobinuria (PNH) and atypical Hemolytic Uremic Syndrome (aHUS) patients

Dosing and Administration

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.

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Preemptive clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

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

ONESOURCE[™]
TREATMENT SUPPORT

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

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

Indications and usage

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

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

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of use

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

Adverse reactions

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

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥15% combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

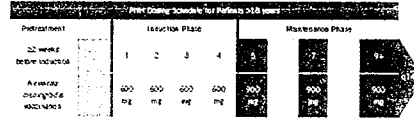
Please see enclosed full Prescribing Information for Soliris, including boxed WARNING regarding serious meningococcal infection.

For patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Soliris® (eculizumab) PNH Dosing Guide

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

Soliris: a chronic therapy for a chronic disease.²



*See date of the administration of the recommended dosing on this page, or visit the date of this time point.

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

- Fixed dose on time is critical to control chronic, complement-mediated hemolysis; for breakthrough hemolysis, dosing may be adjusted to every 12 days instead of 14 days¹
- No dosing adjustments recommended based on age, gender, race, or renal insufficiency¹
- Pre-medications are not routinely required

Monitoring After Discontinuation

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

Important Administration Information

Soliris must be diluted to a final admixture concentration of 5 mg/mL prior to administration.

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

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

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

To learn more about Soliris, please call 1-888-SOLIRIS (1-888-765-4747) or visit www.Soliris.net.

SOLIRIS®
(eculizumab)

For patients with atypical Hemolytic Uremic Syndrome (aHUS)
Soliris® (eculizumab) aHUS Dosing Guide

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

Soliris is a therapy for aHUS—a chronic disease needing chronic treatment¹

Preparation	aHUS Adult (≥18 years) aHUS Dosing Schedule									
	Induction Phase			Maintenance Phase						
20 mg/mL Soliris (200 mg/10 mL)	1	2	3	4	5	6	7	8	9	10-14*
Neisseria meningitidis vaccine	900	900	900	900	1200	1200	1200	1200	1200	1200
Soliris (mg)	900	900	900	900	1200	1200	1200	1200	1200	1200

Body Weight	aHUS Weight-Based Dosing Schedule for Patients ≥18 Years	
	Induction Phase	Maintenance Phase
≤1 kg and over	900 mg weekly × 4 doses	1200 mg at week 5, then 1200 mg every 2 weeks
≤3 kg to less than 40 kg	600 mg weekly × 4 doses	900 mg at week 5, then 900 mg every 2 weeks
≤3 kg to less than 30 kg	600 mg weekly × 2 doses	600 mg at week 3, then 900 mg every 2 weeks
≤3 kg to less than 20 kg	600 mg weekly × 1 dose	600 mg at week 2, then 900 mg every 2 weeks
≤3 kg to less than 10 kg	300 mg weekly × 1 dose	300 mg at week 2, then 600 mg every 2 weeks

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



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

Supplemental dosing of Soliris is required for patients undergoing concomitant plasma therapy¹

Type of Intervention	Most Recent Soliris Dose	Supplemental Soliris Dose With Each PLEX Intervention	Timing of Supplemental Soliris Dose
Plasma exchange or plasma apheresis	1200 mg	900 mg on each day of intervention or on the first day of intervention	Administer on the first day of intervention or on the first day of the next 2 days
Plasma exchange or plasma apheresis	600 mg or more	600 mg on each day of intervention or on the first day of intervention	Administer on the first day of intervention or on the first day of the next 2 days
Plasma exchange or plasma apheresis	300 mg or more	300 mg on each day of intervention or on the first day of intervention	Administer on the first day of intervention or on the first day of the next 2 days

*First day of intervention or first day of the next 2 days of intervention.

Monitoring After Discontinuation

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

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

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS INJECTION.

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

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

¹Plasma therapy = plasma exchange, plasma apheresis, or both therapy modalities (PLEX).

BUSQUO SOLIRIS



For PNH and aHUS

Preparation of Soliris® (eculizumab) for Administration¹

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

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

1. Withdraw the required amount of Soliris from the vial into a sterile syringe and transfer the recommended dose to an infusion bag.
2. Dilute Soliris to a final concentration of 5 mg/mL using the above table as a guideline. The volume of diluent should be equivalent to the drug volume.
3. Gently invert the infusion bag containing the diluted solution to ensure thorough mixture of the product and the diluent.
 - Discard any unused portion left in the vial, as the product contains no preservatives.
4. Inspect visually for particulate matter and discoloration prior to administration.
 - The diluted solution is a clear, colorless liquid and should be practically free of any particles.
5. Allow the admixture to adjust to room temperature prior to administration (18°C-25°C, 64°F-77°F). It must not be heated in a microwave or with any heat source other than ambient air temperature.
6. Admixed solution of Soliris is stable for 24 hours at 2°C-8°C (36°F-46°F) and at room temperature.

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

How Supplied/Storage and Distribution¹

- Vial—30 mL, liquid
- Product strength—10 mg/mL
- Product count—300 mg/30 mL (n=2)
- Product physical space—1 vial per carton
 - Shipped just in time for infusion
 - Weight: <1 lb
 - Dimensions: 1.625" x 1.625" x 3.125"
- Must be stored in the original carton until time of use under conditions at 2°C-8°C (35°F-46°F)
- Protect from light
- DO NOT FREEZE, DO NOT SHAKE
- Do not infuse beyond the expiration date stamped on the carton
- NDC 21682-001-01: Each single-unit carton contains one 30-mL vial of Soliris (10 mg/mL)



→ To enroll in the Soliris REMS and order Soliris, please call 1.888.SOLIRIS (1.888.765.4747)

Daggers code: XXXXXX

Lot #: J1300

Procedure code: XXXXXXXX



Contact Soliris OneSource at 1.888.SOLIRIS (1.888.765.4747)

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

SOLIRIS
(eculizumab)

Storage and Distribution

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with a meningococcal vaccine 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 *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

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

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

References: 1. Soliris® [package insert]. Cheshire, CT: Alexion Pharmaceuticals, Inc.; 2011. 2. Helley D, de Latour RP, Pocher R, et al. French Society of Hematology. Evaluation of hemostasis and endothelial function in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. *Hematologica*. 2010;95:574-581.

ALEXION
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All rights reserved. ALEXION XXX

Appendix 6
REMS website (screenshots)

Soliris REMS Information - Windows Internet Explorer
http://solirisrems-staging.index.html

Favorites Soliris REMS Information

ONESOURCE™ SAFETY SUPPORT

Home | [Prescribing Information](#) | [Medication Guide](#) | [Important Safety Information](#)

Increased Risk of Meningococcal Infection and Soliris: Risk Evaluation and Mitigation Strategy (REMS)

Prescribers must enroll in the Soliris REMS to prescribe Soliris.

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

The goals of the Soliris REMS, the OneSource Safety Support Program, are:

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To inform and educate Healthcare Professionals (HCP) and Patients (or Caregivers, or Legal Guardians) 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.

Physicians prescribing Soliris must enroll in the REMS.

To enroll in the program, download and complete the Prescriber Introductory Letter and Enrollment Form and either drop it in the mail, fax it to Soliris OneSource Safety Support Program at 1-877-580-2596@ (ALXXN); or scan and e-mail it to OSSP@alxn.com.

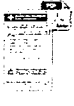
- [Prescriber Introductory Letter and Enrollment Form](#)
- [Patient Introductory Letter and Voluntary Enrollment Form](#)
- [Dosing and Administration Guide](#)
- [Soliris Patient Safety Card](#)
- [Prescriber Brochure, Important Safety Information about Soliris](#)
- [Patient Safety Brochure, Important Safety Information about Soliris](#)

The Soliris Patient Safety Card

Provide your patient with a Soliris Patient Safety Card to carry with them at all times. This safety card contains important safety information about the risk of meningococcal infection that your patient needs to be aware of before they are given Soliris and during their treatment with Soliris. Remind them to show this card to any doctor involved in their treatment.

Tell your patients that if they cannot reach their doctor, go to an emergency room immediately and show emergency room staff the Soliris Patient Safety Card. *Even if they stop using Soliris*, patients should keep their Soliris Patient Safety Card with them for 3 months after the last Soliris dose, since side effects may occur a long time after their last dose of Soliris.

To order a Soliris Patient Safety Information Card, contact OneSource™ at 1.888.SOLIRIS® (1.888.765.4747®).



Soliris REMS Information: Important Safety Information - Windows Internet Explorer

Home | Prescription Information | Medication Guide | Important Safety Information

Important Safety Information

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning.

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with a meningococcal vaccine at least 3 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 Serious Meningococcal Infections for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

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

INDICATIONS AND USAGE

Paroxysmal Nocturnal Hemoglobinuria (PNH)

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

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.

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Limitation of Use

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

CONTRAINDICATIONS

Soliris is contraindicated in:

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

WARNINGS AND PRECAUTIONS

Other Infections

Soliris blocks terminal complement activation, therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. 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.

Monitoring 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 studies, 18 patients (5 in the prospective studies) discontinued Soliris treatment. TMA complications occurred following a mixed 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 reinitiation of Soliris treatment, plasma therapy (plasmapheresis, plasma exchange, or fresh frozen plasma infusion (FFPI)), or appropriate organ-specific supportive measures.

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.

Laboratory Monitoring

PNH

Serum LDH levels increase during hemolysis and may assist in monitoring Soliris effects, including the response to discontinuation of therapy. In clinical studies, six patients achieved a reduction in serum LDH levels only after a decrease in the Soliris dosing interval from 14 to 12 days. All other patients achieved a reduction in serum LDH levels with the 14 day dosing interval [see Clinical Pharmacology and Clinical Studies].

aHUS

Early signs of thrombotic microangiopathy (TMA) include a decrease in platelet count, and increases in serum LDH and creatinine levels. Follow patients for signs of TMA by monitoring serial platelet counts, serum LDH, and creatinine during Soliris therapy and following discontinuation of Soliris.

Infusion Reactions

As with all protein products, 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.

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 sinusitis.

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥15% combined per patient incidence) are hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia.

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

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

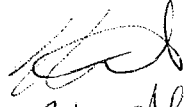
125166s172

OTHER REVIEW(S)

BLA 125166/172
Solirs (eculizumab)

Environmental Assessment

See the Environmental Assessment Review on page 3 of the Product Quality Review.


Ebla Ali Bahar
23 Sep 2011

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

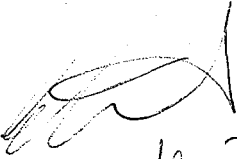
/s/

MARY GRACE LUBAO
08/01/2012

BLA 125166/172
Soliris (eculizumab)

Non-Clinical Review

Non-clinical review not needed for this supplement.

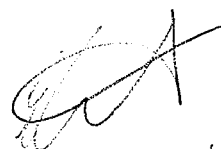


Ebla Ali Ibrahim
23 Sep 2011.

BLA 125166/172
Soliris (eculizumab)

Financial Disclosure Review

See Clinical Reviewer's Review on page 29.

 Ebla Ali Boabain
23 Sep 2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

PATIENT LABELING REVIEW

Date: September 8, 2011

To: Ann Farrell, MD, Director
Division of Hematology (DHP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN *LaShawn Griffiths 9/8/11*
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Barbara Fuller, RN, MSN, CWOCN *Barbara Fuller 9/8/2011*
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Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): Soliris (eculizumab)

Dosage Form and Route: Concentrated solution for intravenous infusion

Application Type/Number: BLA 125166/172

TSI number: 000611

Applicant: Alexion Pharmaceuticals, Inc.

OSE RCM #: 2011-1313

1 INTRODUCTION

The purpose of the Applicant's submission is to seek approval of a labeling supplement proposing a new indication for the treatment of patients with atypical Hemolytic Uremic Syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. The Applicant also submitted a Risk Evaluation and Mitigation Strategy (REMS) modification to include the new proposed indication.

This review is written in response to a request by the Division of Hematology Products (DHP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Soliris (eculizumab). The MG was previously reviewed by DRISK on February 28, 2007.

DRISK Interim REMS Review Comments (Set 1) regarding the proposed REMS modification was sent to DHP under separate cover dated August 22, 2011.

2 MATERIAL REVIEWED

- Draft Soliris (eculizumab) Medication Guide (MG) received on April 5, 2011, revised by the Review Division throughout the review cycle, and sent to DRISK on August 26, 2011.
- Draft Soliris (eculizumab) Prescribing Information (PI) received April 5, 2011, revised by the Review Division throughout the current review cycle and received by DRISK on August 26, 2011.

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. In our review of the MG, the target reading level is at or below an 8th grade 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 APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG 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 DISCUSSION

The Applicant submitted a REMS assessment report on June 1, 2011. We note that the DRISK Interim REMS Review comments dated August 22, 2011, under Recommendations for the Review Division, state that DHP and DRISK agreed that the changes needed in the REMS as a result of deficiencies found in the REMS Assessment report can be accomplished with the REMS modification currently being considered in conjunction with the new indication. Therefore, the PI provided to DRISK for use in our review of the MG for proposed indication reflects changes to the REMS. Our MG revisions address the revisions to the REMS and PI, where appropriate.

5 CONCLUSIONS

The MG is acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated (tracked and clean) versions of the MG are appended to this memo. Consult DRISK 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.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****Pre-decisional Agency Information*****

Memorandum

DATE: AUGUST 29, 2011
To: Ebla Ali Ibrahim, Senior Regulatory Project Manager, DHP
From: Adora Ndu, Regulatory Review Officer, DDMAC  8/29/11
CC: Amy Toscano, DTC Group Leader, DDMAC
Subject: BLA 125166
DDMAC comments for Soliris (eculizumab) Medication Guide

DDMAC has reviewed the proposed Medication Guide for Soliris (eculizumab) submitted for consult on June 22, 2011, and offers the following comments.

The version of the draft Medication Guide used in this review is titled, "26 August 2011 medGuide plr redlined Alexion plus MO revision".

If you have any questions on the patient labeling, please contact Adora Ndu at 301-796-5114 or adora.ndu@fda.hhs.gov.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 29, 2011

Application Type/Number: BLA 125166/172

To: Ann Farrell, M.D., Acting Director
Division of Hematology Products

Through: Zachary Oleszczuk, Pharm.D., Team Leader *Zachary Oleszczuk 8/29/11*
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Carol Holquist, R.Ph., Director *Cecilia Holquist 8/29/11*
Division of Medication Error Prevention and Analysis

From: Cathy A. Miller, M.P.H., B.S.N., Safety Evaluator *Cathy Miller 8/29/11*
Division of Medication Error Prevention and Analysis

Subject: Labels and Labeling Review

Drug Name and Strength: Soliris (Eculizumab) Concentrated Solution For Intravenous Infusion
300 mg/30 mL (10 mg/mL)

Applicant/sponsor: Alexion Pharmaceuticals

OSE RCM #: 2011-1315

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates revisions to Soliris package insert labeling for areas that can contribute to medication errors. The package insert labeling is being revised due to the addition of a new indication for Atypical Hemolytic Uremic Syndrome (aHUS).

1.1 Regulatory History

Soliris (Eculizumab) Solution for intravenous infusion, was approved on March 16, 2008 for the treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH).

On April 29, 2009, Soliris received Orphan Drug Designation (ODD #09-2795) for the potential treatment for patients with atypical Hemolytic Uremic Syndrome (aHUS).

On March 25, 2011, the Applicant submitted a Supplemental Biologic License Application (sBLA) (BLA 125166/172) which proposed a new indication for the treatment of aHUS, along with revisions to package insert labeling to reflect the new indication. The Applicant does not propose any changes to the current commercial container labels or carton labeling.

1.2 Product Information

Soliris is indicated for the treatment of adult patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) to reduce hemolysis. The dose regimen for Soliris is 600 mg via a thirty-five minute intravenous infusion every seven days for the first four weeks, followed by 900 mg for the fifth dose seven days later, and then 900 mg every fourteen days thereafter.

This Soliris supplement proposed the new indication for the treatment of patients with Atypical Hemolytic Uremic Syndrome (aHUS). The dose regimen for adults is 900 mg (b) (4) for the first four weeks, followed by 1200 mg for the fifth dose (b) (4), and then 1200 mg (b) (4). (b) (4) with aHUS, dosing is determined by weight as follows:

- Greater than or equal to 40 kg: 900 mg weekly x 4, followed by 1200 mg at week 5; then 1200 mg every (b) (4)
- 30 kg to less than 40 kg: 600 mg weekly x 2, followed by 900 mg at week 3; then 900 mg every (b) (4)
- 20 kg to less than 30 kg: 600 mg weekly x 2, followed by 600 mg at week 3; then 600 mg every (b) (4)
- 10 kg to less than 20 kg: 600 mg weekly x 1, followed by 300 mg at week 2; then 300 mg every (b) (4)
- 5 kg to less than 10 kg: 300 mg weekly x 1, followed by 300 mg at week 2; then 300 mg every (b) (4)

Soliris is supplied in 300 mg/30 mL vials requiring dilution to a final concentration of 5 mg/mL prior to administration. 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 and 240 mL for 1200 mg doses. Prior to administration, the admixture should be allowed to adjust to room temperature (18°C to 25°C, 64°F to 77°F). The admixture must not be heated in a microwave or with any heat source other than ambient air temperature. Soliris should be administered via intravenous infusion and should not be administered via intravenous push or bolus injection.

2 METHODS AND MATERIALS

Since Soliris has been marketed since 2007, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database to identify any medication errors involving Soliris labels and labeling.

Additionally, DMEPA evaluated the proposed package insert labeling for Soliris using Failure Mode and Effects Analysis¹ (FMEA), principles of human factors, and lessons learned from the post marketing experience to identify areas that can contribute to medication errors.

2.1 SOLARIS ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SELECTION OF CASES

The AERS search conducted June 10, 2011 for Soliris used the following search terms: MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues” along with the active ingredient name of “Eculizumab”, the trade name “Solaris”, and verbatim terms “Soliris%” and “Eculizumab%” without date limitations.

Duplicate reports were combined into cases. Those cases, not pertaining to medication errors were excluded from further analysis (e.g., adverse drug reactions not relating to an error, allergic reactions, wrong infusion rate caused by faulty equipment or attempted suicide). All cases of medication error were evaluated and grouped by the type of error. Each case was evaluated for the root cause.

2.2 LABEL AND LABELING RISK ASSESSMENT

This review focuses on the revised Soliris package insert labeling submitted by the Applicant on April 5, 2011 (no image). The Applicant proposed no revisions to the approved container labels and carton labeling for this product at this time, however, we did reference the approved Soliris labels and labeling retrieved from the Annual Report dated 5/15/2011, in conjunction with the review of the package insert labeling (See Appendix A for images).

3 RESULTS

The following sections describe the findings and analysis of AERS search as well as labels and labeling review.

3.1 SOLARIS ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE RESULTS

DMEPA’s search of the Adverse Event Reporting System (AERS) database retrieved 47 reports, however, seven (n=7) of the reports were found to be not relevant to our review for reasons listed in Section 2.1 and therefore, were not considered further.

The remaining forty (n=40) cases described medication errors associated with the use of Soliris. These errors were grouped into the following types: dose omission, wrong dilution volume, dose omission, wrong time sequence of drug therapy, wrong dilution volume, wrong dose, and wrong frequency of administration. Each type of error is discussed further below (see Appendix B for relevant case narratives).

Dose Omission (n=28)

Twenty-eight (n=28) of the 40 cases involved dose omission of Soliris. In 25 of the 28 dose omission cases, the omissions occurred due to patient non-compliance with the appointment

¹ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

schedule, personal issues including insurance issues, hospitalization with related or other illnesses, or reasons not stated. The remaining three of the 28 dose omission cases occurred where the dose was held due to low blood count (ISR #6200785), poor intravenous access at the time of multiple doses scheduled (ISR 7044854), and due to reported 'mix up with the infusion company' (ISR 6200434).

Wrong Dilution Volume (n=4)

Four (n=4) of the 40 cases involved wrong dilution errors. In all cases, the wrong volume was mixed with the solution, resulting in a wrong final admixed volume (i.e. 1000 mL versus 180 mL, 280 mL versus 180 mL, 180 mL versus 120 mL). In all four of the cases (ISR #6178111, 6177895, 7465821 and 6403942), the volume added was greater than the recommended diluent volume to be added for the scheduled dose, however, in all cases, the correct dose was administered. Because the infusion rate was not specified in the cases, it was not possible to identify whether wrong infusion rate errors occurred with the wrong diluent errors.

Dose Omission and Wrong Dilution Volume (n=1)

One of the 40 cases (ISR #74706232) reported both a dose omission and wrong dilution error. The wrong dilution error involved a volume greater than the correct diluent volume for the scheduled dose (210 mL versus 180 mL), however, the patient did receive the correct dose. Because the infusion rate was not specified in the case, however, it was not possible to identify whether wrong infusion rate errors occurred with the wrong diluent error. The case also reported that the patient 'skipped' a week of therapy but the reasons was not specified.

Wrong Dose (n=5)

Five (n=5) of the 40 cases involved wrong dose errors with Soliris. Three of the five cases (ISR #7467863, 6177915 and 6177734) reported that supply issues (not enough vials available or a vial broke) resulted in the patient being administered an underdose of the scheduled dose. In two of the five cases (ISR #6200638 and 6404143), the wrong titration schedule doses were administered however, no reason for the wrong dose error was specified.

Wrong Time Sequency of Drug Therapy (n=1)

One (n=1) of the 40 cases (ISR #6404068) involved Soliris being administered in the wrong timing sequence with another drug, Eloxatine. Both Soliris and Eloxatine were hung (inverted) at the bedside for in preparation for infusion. However, Soliris 200 mg was administered first, rather than scheduled Eloxatine administration. No adverse events were reported with this error however, prophylactic antibiotic therapy was administered.

Wrong Frequency of Administration (n=1)

One (n=1) of the 40 cases (ISR #6548005) involved the wrong frequency of administration given for the scheduled Soliris dose regimen. The case states that the physician realized that the first 900 mg infusion should have been administered one week after the fourth 600 mg infusion, however, since the dose had already been ordered on a specified date, the patient received the 900 mg dose at that time (prior to seven days). No adverse events were reported with the error.

3.2 LABEL AND LABELING RISK ASSESSMENT

Our evaluation of the proposed package insert labeling identified the following deficiencies:

- The word ‘Concentrated’ that appears in the dosage for (Concentrated Solution for Intravenous Infusion) in the package insert labeling, and on the container label and carton labeling is not consistent with labeling for injection dosage forms.
- The Section 2.2 Preparation and Administration instructions are confusing with regard to the volume of diluent to add based on the scheduled dose versus the desired final admixed volume.
- The patient populations for PNH (not specified as ‘adult’), and aHUS pediatrics (only specified as (b) (4) with no other age ranges, can be more clearly specified in the Highlights and Section 2 Dosage and Administration section.
- Package insert labeling includes the use of the dangerous abbreviations < and >.
- No Medication Guide statement appears on the principal display panel of the container label or the carton labeling in accordance with 21 CFR 208.24(2)(d).

4 DISCUSSION

This section discusses issues related to vulnerabilities identified with Soliris labels and labeling, along with medication errors associated with the product.

4.1 MEDICATION ERRORS

DMEPA identified dose omission, wrong dilution volume, dose omission, wrong time sequence of drug therapy, wrong dilution volume, wrong dose, and wrong frequency of administration medication errors. However, our analysis determined that most of the errors were a result of practice related issues and not the approved labels and labeling, with the exception of medication errors associated with wrong dilution volume added during preparation. For these errors, DMEPA found that medication errors may be associated with ambiguities in the package insert labeling Section 2.2 Preparation and Administration section directives for diluting the product. We discuss this issue further below.

The Preparation and Administration Section 2.2 of the package insert labeling that describes the admixture volume for dilution is confusing and may be contributing to the wrong dilution volume medication errors. The section reads “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.” We believe that clinicians may be misinterpreting the ‘final admixed volume’ amount with the amount needed to add during dilution, which results in a volume in excess of the recommended total admixed volume. This section can be improved by providing clearer directives about the amount of diluent to be added based on the scheduled dose.

DMEPA also found that the use of the term ‘Concentrated’ in the presentation of the dosage form for this product (Concentrated solution for Intravenous Infusion). We consulted with the biologics quality reviewer for this product, along with our ONDQA staff, for input on this issue. The review team explains that the word ‘concentrated’ was originally intended to indicate that the drug must be diluted prior to use but agrees that there is inconsistent use of the word ‘concentrated’ for other similar products that require dilution prior to administration. ONDQA cited that the use of the word ‘concentrated’ does not follow the conventional USP nomenclature use of the word ‘concentrated’ and is not an acceptable dosage form modifier. We note that our review of AERS cases did not identify any cases of maladministration that involved infusing Soliris without diluting prior to administration. Our review of container labels and carton labeling found that the statement “must be diluted prior to use” does appear on carton labeling, however, the statement appears on the side panel, and no statement appears on the container label. DMEPA believes this statement should be conspicuously displayed on the principal display panel

of the carton labeling and if space permits, should also appear on the container label. However, since DMEPA recognizes that Soliris is already a marketed product which utilizes the dosage form name “Concentrated Solution for Intravenous Infusion”, we defer to the DHP review team to make decisions about the dosage form language.

DMEPA found that the package insert labeling includes the use of the error-prone abbreviations < and > used in the presentation of the weight ranges in the Highlights and Section 2 Dosage and Administration sections. These symbols have been identified by ISMP as dangerous abbreviations that have contributed to medication errors and should be eliminated.² Specifically, if the < is inadvertently interpreted as ‘greater than’, rather than the intended ‘less than’, or vice versa, this confusion could lead to wrong dose medication errors.

DMEPA also considered whether the new indication of aHUS introduces vulnerabilities that may result in medication errors. When new indications are added to an existing product, DMEPA evaluates whether confusion may occur in the clinical setting since the same product will be used to treat different disease states, with varying dosing regimens and patient populations. We evaluate whether these factors warrant separate product labeling for the different indications and whether considerations should be given to proposing a different proprietary name for the new indication. Dosing varies between the two indications with aHUS adult dosing beginning at 900 mg, and a maintenance dose of 1200 mg, and weight-based dosing for pediatric and adolescent patients. Dosing for PNH includes adult dosing beginning dose of 600 mg, with a maintenance dose of 900 mg and does not include dosing for pediatric or adolescent patients. Although the dosing regimens vary, we believe that the dosing schedules, including each stage of the dosing regimen, the frequency of administration, and the patient populations, are clearly presented in product labeling. Because both indications, PNH and aHUS, are rare hematological conditions with some similar etiologies and disease manifestations, we found that it seems reasonable to managed both indications under the same labeling and proprietary name, and that variations in dosing and patient populations can be distinguished through product labeling, as currently presented in the proposed package insert labeling. However, we recommend clarifying that PNH dosage regimen is for ‘Adults’, and clarifying the pediatric age range, currently presented as (b) (4) in the Dosage and Administration section, to assure clarity in the patient populations and minimize the potential for dosing errors, and we have provided our recommendations below in Section 5.1.

Lastly, DMEPA found that there is no medication guide statement on the principal display panel of the carton labeling, in accordance with 21 CFR 208.24(2)(d). A statement that reads “See package insert for dosage, dilution, and administration instructions” appears on the side panel of the carton labeling but this statement does not specifically identify the “Medication Guide” and it does not appear on the principal display panel. This statement should be added in accordance with the regulation, in order to readily alert clinicians about the distribution of the product’s Medication Guide, and therefore, we have provided recommendations below in Section 5.2.

5 CONCLUSIONS AND RECOMMENDATIONS

The proposed package insert labeling for the new indication of aHUS can be improved to describe the dosage form without the use of the unconventional use of the modifier ‘concentrated’, to illustrate the correct dilution volume for the schedule dose, to identify the patient population for the PNH versus aHUS populations, to describe the weight-based dosing without the use of error-prone abbreviations. We also found that improvements can be made to

² ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations included on jcaho.org “Do Not Use” list effective January 1, 2004. www.ismp.org

the container labels and carton labeling to alert practitioners that the product includes a Medication Guide that should be distributed to the patient, and that the product should be diluted prior to administration. Section 5.1 *Comments to the Division* contains our recommendations regarding recommended revisions to the package insert labeling. Section 4.2 *Comments to the Applicant* contains our recommendations for revisions to the container label and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

5.1 COMMENTS TO THE DIVISION

We have reviewed the proposed package insert labeling submitted by the Applicant for the proposed indication of aHUS and have the following recommendations:

1. Revise the Section 2.2 Preparation and Administration to more clearly describe the correct dilution volume based on the dosing regimen. Our review of AERS identified wrong dilution volume medication errors that occurred because clinicians added the wrong amount of diluent (over the recommended amount) resulting in an admixed volume in excess of the correct amount for the scheduled dose. We recommend a table that provides clear dilution directives to appear below the three bulleted instructions in the first paragraph such as the one below:

Soliris Dose	Volume of Diluent Added	Final Admixed 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

2. Remove the abbreviations '<' and '>' used in the highlights and Section 2 Dosage and Administration section. These symbols have been identified by ISMP as dangerous abbreviations that have contributed to medication errors. Specifically, if the < is inadvertently interpreted as 'greater than', rather than the intended 'less than', or vice versa, this confusion could lead to wrong dose medication errors.
3. Revise the Highlights and Section 2 Dosage and Administration section to clarify the patient populations as follows:
 - For PNH Dosage Regimen: Add the word 'Adult'. According to the Clinical Trials section, the PNH indication was studied in the adult population, and since the proposed new indication of aHUS is for pediatric and adolescent patients, it is important to clarify that the PNH indication is only for adults.
 - For aHUS Dosage Regimen: Define the (b) (4) population with more specific age ranges. We found that the adolescent patient population is clearly defined to be the ages of 12 years old to 18 years old, however, the pediatric patient population is defined only as (b) (4). If there is a minimum age limit for the pediatric patient population, the age limit should be more clearly defined.

5.2 COMMENTS TO THE APPLICANT

DMEPA has the following additional recommendations for revisions to Soliris container labels and carton labeling. We request that the Applicant implement these revisions at the time of the next printing as follows:

1. Add a Medication Guide statement to the principal display panel of the carton labeling in accordance with 21 CFR 208.24(2)(d).
2. Relocate the statement “Must be diluted prior to use” to the principal display panel of the carton labeling, and if space permits, add this statement to the principal display panel of the container label. We believe this may be accommodated by decreasing the size of other elements on the principal display panel of the container label including the established name, and relocating the ‘Rx Only’ to the side panel of the label.
3. Revise the statement “Single-Use Vial” that appears on the principal display panel of the container label to read “Single-Use Vial – Discard Unused Portion”.

6 REFERENCES

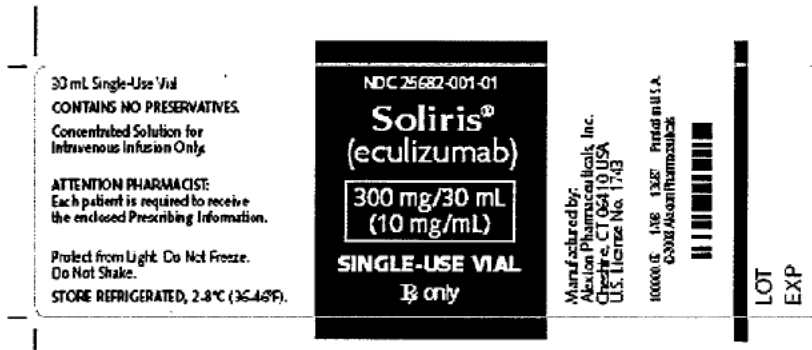
1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported

Appendices

Appendix A: Soliris Approved Container Labels and Carton Labeling (Retrieved from the Annual report dated 5/16/2011)

Container Label



Carton Labeling



Appendix B: Relevant Medication Error Cases (n=40)

ISR NUM	RECV DATE	Narratives	Medication Error Type
6200838	5/22/09	A 40 year-old female initiated treatment with intravenous Soliris for paroxysmal nocturnal hemoglobinuria (PNH). She received the initial 600 mg infusion on 10JUL2007 with additional 600 mg infusions on 17JUL2007, 24JUL2007 and 31JUL2007, and 900 mg infusions on 07AUG2007, 21AUG2007, 04SEP2007, 25SEP2007, 08OCT2007, 22OCT2007, 08NOV2007, 20NOV2007, 04DEC2007, 18DEC2007, 01JAN2008, 08JAN2008, 22JAN2008, 05FEB2008, 19FEB2008, 04MAR2008, 19MAR2008, 01APR2008, 15APR2008, 29APR2008, 19MAY2008, 02JUN2008, and 12JUN2008. On an unknown date in 2008, the patient was hospitalized for an unknown event. Medical history included PNH. Concomitant medications were unknown. Follow-up information was received on 26JUN2008 from a nurse. The patient was hospitalized due to an unspecified access port infection. Treatment provided and outcome was unknown. Follow-up information was received on (b) (6) from the consumer's daughter. The consumer had just gotten out of the hospital after being admitted one and a half weeks ago for low blood count, a stroke, and a mild heart attack. Follow-up information was received on 29SEP2008 from a nurse at the physician's office. The patient received additional Soliris infusions on 19MAY2008, 30MAY2008, and 13JUN2008. The patient also received a 900 mg Soliris infusion on (b) (6). The patient was hospitalized and then discharged. <u>She did not show for her appointment and missed her infusion on 26JUN2008. The patient did not show for her scheduled appointment on 24SEP2008 and attempts to contact her were unsuccessful.</u>	Dose Omission.
6200853	5/23/09	A male patient initiated treatment with intravenous Soliris. Infusion dates and indication were not provided. In (b) (6), the patient underwent knee surgery without complications. The patient's hemolysis was well controlled by Soliris. Medical history included hemolysis. Concomitant medications were not provided. Follow-up was received on 29SEP2008 from a physician. The patient initiated Soliris 600 mg in JUN2008 for paroxysmal nocturnal hemoglobinuria (PNH). Additional administration dates were not provided. The patient had a history of arthritis before starting Soliris. On 15AUG2008, he underwent a knee replacement due to arthritis of the knee. The surgery had been scheduled prior to initiation of Soliris therapy. The patient was subsequently hospitalized for five to six days. The knee arthritis was considered resolved with treatment on 15AUG2008. The physician specified that the patient had had no reaction to Soliris. Additional medical history included PNH, aplastic anemia, hepatitis C, type-2 diabetes mellitus, arthritis, and posttraumatic distress syndrome (PTSD). Causal relationship to Soliris was not provided. Follow-up was received on 07OCT2008 from a physician. This 59 year-old patient received the initial Soliris 600 mg infusion on 11APR2008 with additional infusions on 18APR2008, 25APR2008 and 02MAY2008, and 900 mg infusions on 09MAY2008, 23MAY2008, 16JUN2008, 27JUN2008, 10JUL2008, 24JUL2008, 07AUG2008, (b) (6), 04SEP2008, 18SEP2008, and 06OCT2008. <u>The 06JUN2008 infusion was missed due to the patient being on vacation.</u> The (b) (6) infusion was administered while the patient was in the hospital. The patient underwent knee surgery on (b) (6), not 15AUG2008, and the event was considered resolved the same day as the surgery. The physician confirmed that the surgery was scheduled prior to starting Soliris and that the pre-existing arthritis did not worsen after Soliris initiation. The physician considered the event not related to Soliris. Additional medical history included hypertension and erectile dysfunction. Concomitant medications included prednisone, folic acid, hydrochlorothiazide, insulin, vardenafil, morphine, oxycodone, lisinopril, and amlodipine.	Dose Omission

ISR NUM	RECV DATE	Narratives	Medication Error Type
6200054	5/22/09	A 32 year-old male patient initiated treatment with intravenous Soliris for paroxysmal nocturnal hemoglobinuria (PNH). The initial 600 mg infusion was received on 09MAY2007 with additional 600 mg infusions on 16MAY2007, 23MAY2007, and 30MAY2007. The patient received infusions of Soliris 900 mg on 06JUN2007, 20JUN2007, 04JUL2007, 18JUL2007, 08AUG2007, 22AUG2007, and 05SEP2007. In AUG2007, the patient reported a return of PNH symptoms, which included tingling to upper arms and thighs, insomnia, headaches, eyes strain, jaundice of sclera, and hematuria described as dark orange urine. The consumer also reported a 16-pound weight gain since AUG2007. In SEP2007, the patient experienced shortness of breath. On 26SEP2007, he experienced profuse sweating which lasted 15 minutes. Outcome of the weight gain, feeling of fullness, and shortness of breath was unknown. The PNH symptoms remained ongoing. The patient was seen by the physician on 07SEP2007 and was prescribed Ambien for sleep. A liver ultrasound was done in SEP2007 and was normal. Medical history included PNH characterized by hematuria, tingling to the upper arms and thighs, insomnia, headaches, eyestrain, and jaundice of sclera. Concomitant medications were not provided. Follow-up information was received on 07NOV2007 via phone from a certified pharmacy technician. The patient received additional 900 mg infusions of Soliris on 21SEP2007, 05OCT2007, 19OCT2007, and 05NOV2007. On 07SEP2007, the patient experienced shortness of breath, lightheadedness, insomnia, a sensation of being full, and a 16-pound weight gain. The patient received Ambien for the insomnia. An ultrasound of the liver was done on 12SEP2007 to rule out thrombosis, which was negative. On 21SEP2007, the patient's lactate dehydrogenase (LDH) level increased to 1542 U/L. LDH levels had been 909 U/L on 22AUG2007 and 531 U/L on 07SEP2007. Liver function tests were normal on 21SEP2007. On 28SEP2007, the patient experienced dark urine and pain in his arms, legs, and chest. No treatment was provided. On 03NOV2007, the patient experienced intermittent kidney pain. The patient felt that the kidney pain might be due to delay in Soliris treatment, which was due on 02NOV2007, but was delayed until 05NOV2007. On 05NOV2007, LDH level was 521 U/L. The shortness of breath, lightheadedness, insomnia, sensation of being full, dark urine, and pain in his arms, legs, and chest resolved on 05OCT2007. By 19OCT2007, the patient's weight had stabilized. The increased LDH level was resolved on 05NOV2007. The intermittent kidney pain was ongoing. Concomitant medications included cetirizine hydrochloride (Zyrtec), guaifenesin (Mucinex), diphenhydramine hydrochloride (Benadryl), simethicone (Gas-X), and paracetamol (Tylenol). Follow-up information was received on 09JAN2008. The patient received additional 900 mg Soliris infusions on 16NOV2007, 30NOV2007, 14DEC2007, and 02JAN2008. The patient experienced weight gain since AUG2007. He weighed 238 pounds on 01AUG2007 and was 276 pounds on 09JAN2008. In SEP2007, he also experienced occasional constipation and yellow sclera with red rims. He treated the constipation with citrate of magnesia as necessary. No treatment was received for the yellow/red sclera. In NOV2007, he experienced intermittent flank pain, which was described as kidney pain or back pain, and was treated with oxycodone/paracetamol (Roxicet). When the Roxicet prescription was gone he used acetylsalicylate acid/caffeine (Bayer Extra Strength) 500 mg daily. Additionally, he experienced a cold in DEC2007. In DEC2007, the patient took azithromycin (Z-pak), and then developed a cold and sinusitis for which he received another Z-pak in the same month. In DEC2007, he experienced a gradual loss of hand and arm strength. All events were ongoing. Additional medical history included removal of his uvula in (b) (6). Also, he moved to a new home in late AUG2007 and the home was positive for mold. The patient attributed his symptoms of dizziness, insomnia, and shortness of breath to the presence of the mold, because the symptoms resolved, in OCT2007, once the mold was removed. Follow-up information was received on 24JAN2008: The patient received an additional 900 mg Soliris infusion on 18JAN2008. The patient's weight gain started in AUG2007 and flank pain, confirmed as lower back pain, since NOV2007 were ongoing. The patient had gained 30 pounds over six months. The physician recommended that the patient increase his exercise by 10 minutes a day and see a nutritionist. The patient remained on a calorie-restricted diet. On 16JAN2008, the patient's eyes were clear with no yellow sclera and the physician could not confirm that the patient experienced yellow sclera, dizziness, shortness of breath, constipation, or loss of hand and arm strength. On an unspecified date, the patient experienced sleep apnea and overall lethargy, which were ongoing. The physician attributed the overall lethargy and weight gain to sleep apnea. The patient will see a laryngologist for treatment of sleep apnea. The physician indicated that the events of weight gain, sleep apnea, back pain, and overall lethargy were not related to Soliris. Follow-up information was received on 25FEB2008. The patient received additional 900 mg Soliris infusions on (b) (6) and 18FEB2008. In (b) (6), the patient was hospitalized for elective surgery to insert an unspecified ENT (ears, nose, throat) prosthesis due to the previous removal of his uvula. He received treatment with Roxicet after surgery. On (b) (6), five days after his last Soliris infusion, the patient was rehospitalized to replace the prosthesis. On 12FEB2008, the patient experienced a fever and hemolysis, which was characterized by three days of rose-colored urine. On 15FEB2008, his urine color changed to black. <u>The patient missed his Soliris infusion scheduled for 15FEB2008 due to issues with his mouth.</u> On 19FEB2008, one day after his last Soliris infusion, the patient experienced bad breath that he described as "stunk like bad	Dose Omission

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		meat". He then began coughing up yellow-green phlegm and while he was coughing his ENT prosthesis fell out. On 20FEB2008, the patient presented to a walk-in clinic and was diagnosed with oral bacterial and oral yeast infections. He received treatment with oral nystatin solution four times daily until finished and oral erythromycin 500 mg daily for six days. On 20FEB2008, the hemolysis resolved. The outcomes of the fever, bacterial infection, yeast infection, bad breath, the ENT prosthesis falling out, and coughing up yellow-green phlegm were not reported. Additional medical history included an unspecified ENT birth defect. Follow-up was received on 21JUL2008 from the patient. The patient received additional 900 mg Soliris infusions on 29FEB2008, 14MAR2008, 28MAR2008, 11APR2008, 25APR2008, 09MAY2008, 23MAY2008, 05JUN2008, 19JUN2008 and 03JUL2008. On an unknown date in 2008, within two to three days of the next Soliris infusion, the patient experienced a return of his PNH symptoms, which included sclera color change, back pain, fatigue, and tingling sensation to upper arms and thighs. The symptoms would resolve within one to two days after Soliris infusions but continued to recur. The last episode resolved on 05JUL2008. The patient declined to have his physician contacted for further information. Follow-up information was received on 30JUL2008 from the consumer. The consumer received an additional 900 mg Soliris infusion on 30JUL2008. On 28DEC2007, the consumer missed his 900 mg Soliris infusion. The infusion was received on 02JAN2008. On an unspecified day in JUL2008, the consumer experienced breakthrough hemolysis described as "coke-colored urine" and bilateral back pain in the kidney area, which was worse on the right side. On 17JUL2008, the consumer missed his infusion. On 29JUL2008, the consumer experienced right lower leg pain with a warm calf. The leg pain improved and the warm calf resolved on the same day. On 30JUL2008, the patient received the 900 mg infusion. The breakthrough hemolysis was ongoing. Medical history was negative for thrombosis or deep vein thrombosis (DVT). Follow-up was received on 08OCT2008 from the physician. The patient received additional Soliris infusion at the end of JUL2008 and on 27AUG2008. On 06AUG2008, during a follow-up visit with his physician, the patient had no complaints. He had received a Soliris infusion the week before. Blood pressure was 124/90 mmHg (100-120/60-80). Weight was 248 pounds. There had been no recent weight change. The patient still had hematuria. Additionally patient had constipation on iron therapy. Laboratory results revealed a hemoglobin level of 11.3 g/dl (12-16), and hematocrit of 33.9% (37-47). The patient was to be referred to another physician for bone marrow transplant (BMT). Soliris infusions were scheduled for 13SEP2008 and 27SEP2008. As of the next follow-up visit on 03SEP2008, the patient had not yet made the appointment for his bone marrow transplant consult. His blood pressure was noted to be elevated at 142/90 mmHg in the right arm and 144/90 mmHg in the left arm. Weight was 250 pounds; hemoglobin was 13.1 g/dl, and hematocrit 38.1%. The next Soliris infusions were scheduled for 10SEP2008, 24SEP2008, 08OCT2008, and 29OCT2008.	
6404054	10/16/09	This report was received from a physician on 01SEP2009, with follow-up on 08SEP2009 and 09SEP2009, and from a nurse on 16SEP2009. A patient (gender and age not provided) initiated treatment with intravenous Soliris (eculizumab). He received the first infusion in 2007. Most recent administration schedule was 1200 mg every two weeks. The physician reported that on an unspecified date, the patient switched insurance companies. At the time of this reporting, the patient had been off treatment for approximately eight weeks. The patient received his first re-induction dose on 09SEP2009. Medical history and concomitant medications were not provided. The nurse reported that the patient is a 43 year-old male initiated treatment with intravenous (IV) Soliris (eculizumab) for paroxysmal nocturnal hemoglobinuria (PNH). He received a second 600 mg Soliris infusion on 16SEP2009. He was scheduled to receive a third 600 mg infusion, then a 900 mg infusion, followed by a 1200 mg infusion every two weeks. <u>The nurse confirmed that the patient missed the Soliris infusions due to a lack of insurance and not due to any adverse event.</u> It was unknown if the patient experienced any event during the period of missed infusions. The patient was described as very quiet and not reporting things to his physician or to the nurses. Medical history includes PNH.	Dose Omission

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6677887	4/12/10	This report was received from a physician on 03MAR2010. A 53-year-old male patient received intravenous Soliris (eculizumab). At the time of reporting he was receiving a maintenance dose of 900 mg every 14 days. On 10FEB2010, <u>the patient missed a scheduled Soliris infusion due to a snow storm</u>, and was unable to get transportation to the infusion site the next day. The patient had a comorbidity of cerebral palsy (CP) and required special transportation arrangements to get to his infusion site. On (b) (6), he experienced symptoms of hemoglobinuria, and on (b) (6) he was hospitalized and treated with steroids and fluids for hydration. On 17FEB2010, the patient received his Soliris infusion one week late. On (b) (6), the patient again experienced breakthrough hemoglobinuria and was sent to the emergency room. On (b) (6) the patient received his Soliris dose one day early. Soliris therapy was ongoing. No further information was provided. Medical history included a comorbidity of CP. Prior to missing the Soliris dose on 10FEB2010, the patient was described as doing 'beautifully'. Concomitant medications were not provided. The reporting physician did not report the causal relationship of the breakthrough hemolysis and missed dose to Soliris therapy. Follow-up information was received on 18MAR2010 from a healthcare professional (nurse). The nurse reported that the hemolysis did not stop after the 17FEB2010 dose of Soliris. She noted that the patient was hospitalized for three or four days (exact dates were not known) and noted that the physician thought this would conclude with the next dose on 02MAR2010, but hemolysis continued. Additionally, the patient complained of abdominal pain and increased fatigue. The nurse reported that she did not see the patient's urine and could not say if he had hemoglobinuria. She also reported that the patient was a poor historian. On 10MAR2010, the patient returned to induction dosing, receiving a 600 mg Soliris infusion. He received an additional 600 mg Soliris infusion on 17MAR2010. She reported that the plan was to continue 600 mg Soliris infusions on 24MAR2010 and 31MAR2010, then increase the dosage to 900 mg on 07APR2010 and continue 900 mg dosing schedule on 21APR2010, if tolerated. The outcomes of hemoglobinuria, abdominal pain and increasing fatigue were not reported. Additional medical history included the patient being wheelchair bound and a poor historian. The nurse did not report the causal relationship of hemoglobinuria, abdominal pain and increasing fatigue to Soliris therapy. Follow-up information was received on 26MAR2010 from a healthcare professional (nurse). The patient received Soliris therapy for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). The most recent infusion was noted to be 600 mg on 24MAR2010. On (b) (6), the patient experienced hemoglobinuria and was hospitalized. Also in (b) (6), during hospitalization, the patient experienced abdominal pain and increasing fatigue. It was not known by the nurse whether the patient received treatment for the abdominal pain and/or increasing fatigue. The abdominal pain resolved in FEB2010, and the hemoglobinuria and increasing fatigue resolved in MAR2010, after Soliris therapy was restarted. Medical history included PNH. The patient had no history of fatigue. Concomitant medications included prednisone, amlodipine (Norvasc), lansoprazole (Prevacid), and tamsulosin (Tamsulosin). The reporting nurse considered the abdominal pain, increasing fatigue, and hemoglobinuria unrelated to Soliris therapy. Company Comment 26MAR2010: Upon receipt the follow up information, the case maintains a serious (hospitalization), medically confirmed, report of hemolysis and dehydration. Both events are unlisted in Company Core Data Sheets. The rest of the reported events also reported were non-serious. Citing the underlying disease, the company considers the events as unlikely related to Soliris as the omission of the dose plays most reasonable alternative explanation. US-ALEXION-A201000246	Dose Omission
6200789	5/22/09	A 53-year-old male initiated treatment with intravenous (IV) Soliris for paroxysmal nocturnal hemoglobinuria (PNH). He received the initial 600 mg infusion on 24APR2008 with additional infusions on 01MAY2008, 07MAY2008 and 14MAY2008, and 900 mg infusions on 21MAY2008, 05JUN2008, 19JUN2008 and 03JUL2008. In JUL2008, after the eighth infusion, the patient developed a generalized maculopapular rash. Treatment and outcome of the rash were unknown. The patient's medical history included PNH, acute renal failure, myocardial infarction, seizures, and hypertension. Concomitant medications included folic acid, calcium and levetiracetam (Keppra). Follow-up was received on 30JUL2008 from a physician. <u>On 17JUL2008, the patient missed his 900 mg Soliris infusion, which was administered on 25JUL2008.</u> On 08JUL2008, blood work showed a haptoglobin level of 73 and an increased lactate dehydrogenase (LDH) of 318, up from the lowest value of 250 on 05JUN2008. On 25JUL2008, LDH was 340, protein level 7, alkaline phosphatase 105, and total bilirubin 0.5. On (b) (6), the patient was hospitalized with a pulmonary embolism and bilateral leg deep vein thrombosis (DVT). Blood work done on the same day showed a white blood cell count (WBC) of 4.9, hemoglobin of 12, platelet count of 171, blood urea nitrogen (BUN) of 20, and creatinine of 1.2; LDH results were pending. Treatment was unknown. The outcome of increased LDH was unknown. The pulmonary embolism and the bilateral DVT of legs were ongoing. The patient was still hospitalized at the time of this report. Follow-up information was received on 26AUG2008 from a physician. On (b) (6), a venous study of both legs showed acute deep vein thrombosis of right profunda femoral vein, superficial femoral vein, popliteal vein, and posterior tibial and peroneal vein. On the left, he had acute thrombus in the left profunda femoral vein and left popliteal vein. A CT scan of the chest showed bilateral pulmonary emboli in the left	Dose Omission

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		lower lobe, distal right main pulmonary artery, and the left lower lobe. The patient received treatment with subcutaneous enoxaparin sodium (Lovenox) 1 mg/kg every 12 hours and warfarin sodium (Coumadin). On (b) (6), he had placement of a trapeze inferior vena cava filter via the right internal jugular vein. His leg pain improved. On (b) (6), his international normalized ratio (INR) was 1.5, hemoglobin 10.9, and platelets 189000. He was discharged from the hospital on (b) (6) and was to continue Lovenox and Coumadin after discharge. Additional medical history included a transient ischemic attack, a non-obstructive pulmonary embolus of the right lower lobe in (b) (6), thrombocytopenia, severe intravascular hemolysis, and a ventral hernia. Additional concomitant medications included pantoprazole (Protonix), prednisone, metoprolol, hydrochlorothiazide, potassium chloride (K-Lor), hydroxyzine (Atarax), cetirizine hydrochloride (Zyrtec), and clindamycin. The physician assessed the skin rash to be likely due to Soliris or prednisone.	
j200905	5/23/09	A 64 year-old male initiated treatment with intravenous Soliris for paroxysmal nocturnal hemoglobinuria (PNH). He received the initial 600 mg infusion on 28JAN2008 with additional 600 mg infusions on 04FEB2008, 11FEB2008 and 18FEB2008. He received 900 mg infusions on 25FEB2008, 10MAR2008, 24MAR2008, 07APR2008, 21APR2008, 05MAY2008, 19MAY2008, 02JUN2008, 16JUN2008 and 30JUN2008. In (b) (6), the patient presented to the Emergency Room (ER) with atrial fibrillation. A successful cardioversion was performed and he was released from the ER the same day. Unspecified blood tests were performed in the ER, but the results were unknown. The patient's medical history included PNH, polycythemia, hypertension, bleeding gastric ulcers, and splenectomy. Concomitant medications included warfarin sodium (Coumadin), prednisone, metoprolol succinate (Toprol XL), and hydroxycarbamide (Hydrea). Follow-up was received on 22JUL2008 from the patient's wife. The atrial fibrillation started on (b) (6). On (b) (6), the patient went to the ER and was subsequently hospitalized. Initial treatment with unspecified medications was unsuccessful. On (b) (6), a successful cardioversion was performed and the patient converted into normal sinus rhythm. The patient had a history of ascites, prior to starting Soliris treatment; on (b) (6), soon after the cardioversion, the ascites returned. The patient was discharged home on (b) (6). He had an appointment with a cardiologist on (b) (6). The ascites was ongoing. Additional medical history included portal vein clot prior to Soliris, stent placement over 10 years ago, and ascites in (b) (6), drained prior to Soliris. Follow-up was received on 07AUG2008 from a cardiologist. The physician confirmed the atrial fibrillation and ascites diagnoses. There were no relevant laboratory test results. Another physician provided treatment for the ascites. The cardiologist assessed the relationship of the atrial fibrillation as doubtfully related to Soliris, as atrial fibrillation is quite common in patients of this age with arteriosclerotic heart disease (ASHD). The physician indicated that the causality for the recurrent ascites was unclear. Follow-up information was received on 14AUG2008 from a consumer. The consumer was admitted to the hospital on (b) (6) with a fever. Culture results up to (b) (6) had been negative. The consumer received blood transfusions while hospitalized. Follow-up information was received on 21AUG2008 from the consumer's wife and from a nurse. The patient received additional Soliris 900 mg infusions on 14JUL2008, 28JUL2008, and (b) (6). The patient was admitted to the hospital on (b) (6) for ascites and a paracentesis was done on (b) (6) that removed 2.7 liters of fluid. The patient was discharged on (b) (6). On 04AUG2008, as an outpatient, the patient had paracentesis with 3 liters of fluid removed. The patient's baseline lactate dehydrogenase (LDH) was 4872 in DEC2007 and his hemoglobin level was 8.2 g/dL on 21JAN2008 before Soliris was started. The patient's LDH level was 3338 in (b) (6). The patient experienced dark urine and fatigue two to three days before each Soliris infusion since starting Soliris. On 09AUG2008, the patient had dark urine that continued until he received Soliris on (b) (6). On (b) (6), the patient was hospitalized with a fever of 100.8 degrees to 101 degrees. Blood, urine and stool were negative for infection. A diagnosis for the fever was not determined. The patient received treatment with oral acetaminophen (Tylenol) and intravenous ampicillin 3 grams for seven days. He also received six units of blood between (b) (6) and (b) (6). His hemoglobin levels were 8.9 g/dL on (b) (6) and 9.4 on (b) (6). <u>The patient missed his scheduled Soliris infusion on 1 (b) (6).</u> He was discharged from the hospital on (b) (6) and received a Soliris infusion on the same date. On (b) (6), he was admitted to a different hospital with clots in his portal and hepatic veins. An ultrasound showed perfusion in two liver vessels. A magnetic resonance imaging scan showed clots in the portal and hepatic veins. He received tissue plasminogen activator (TPA) treatment and remained hospitalized at the time of	Dose Omission

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		the report on (b) (6). The fever resolved or (b) (6). The ascites and the clots in the portal and hepatic veins were ongoing. The patient's medical history included polycythemia vera, splenic infarct, wound dehiscence, methicillin-resistant staphylococcus aureus (MRSA), coronary stent placement, atrial fibrillation and gastrointestinal bleed. Additional concomitant medications included folic acid, hydroxyurea, and esomeprazole magnesium (Nexium). Follow-up was received on 28AUG2008 from a nurse. The nurse confirmed that the patient was hospitalized for ascites on (b) (6), underwent fluid removal on 04AUG2008, was hospitalized for fever and clots in the portal and hepatic veins or (b) (6), that he received blood transfusions in (b) (6), and that he experienced dark urine and fatigue two to three days before each Soliris infusion. The nurse believed that the patient was still hospitalized. Follow-up was received on 08SEP2008 from the patient's wife. While hospitalized, the patient experienced gastrointestinal (GI) bleed. No further information was provided. Follow-up was received on 19SEP2008 and on 26SEP2008 from the patient's wife and from a physician. The patient's wife reported that her husband ruptured blood vessels in his back while hospitalized. He underwent surgery to cauterize the vessels or (b) (6). Soliris therapy was ongoing. The physician confirmed the GI bleed. An endoscopy was performed. The GI bleed prolonged the hospitalization and resolved on (b) (6) after discontinuation of acetylsalicylic acid (aspirin) and fondaparinux sodium (Arixtra). No other treatment was rendered. On (b) (6), the patient experienced shoulder hematoma, which was resolving. The patient remained hospitalized. On (b) (6), he received a dose of Soliris, and the next day his temperature was 103 degrees. Culture results came back positive for Listeria. Corrective treatment included vancomycin and intravenous Zosyn. As per the physician, the events GI bleed and shoulder hematoma were not related to Soliris. The patient had a history of bleeding ulcers and the GI bleed was attributed to anticoagulants. The hematoma was considered a bleeding complication. Follow-up information was received on 04NOV2008 from a physician. The patient was maintained on Soliris throughout hospitalization (b) (6) receiving infusions every 12 days, and then every 10 days. On (b) (6), the patient spiked a high fever. A blood culture drawn on (b) (6) was positive for pansensitive Listeria. The Listeria infection and pyrexia resolved on (b) (6) after treatment with antibiotics. The patient was discharged from the hospital on (b) (6). Discharge medications included Nexium, Arixtra, Hydrea, and prednisone. The physician assessed the Listeria and pyrexia as possibly related to Soliris in the setting of prior splenectomy. The patient was the index case of a three-person outbreak of Listeria infection at the hospital. The source of the infection was presumed to have been some food products sold at the hospital, but the actual source was unclear.	
6200833	5/22/09	A 56 year-old male initiated treatment with intravenous (IV) Soliris for paroxysmal nocturnal hemoglobinuria (PNH). He received the initial 600 mg infusion on 07MAY2008 with an additional infusion on 14MAY2008. On 07MAY2008 and 14MAY2008, after each Soliris infusion, the patient experienced feeling sleepy and feeling weak. Both events resolved in MAY2008. Prior to initiating Soliris, the patient's hemoglobin level was 8.8 and lactate dehydrogenase (LDH) was 1645. On 14MAY2008, hemoglobin level was 9.2. The patient's medical history included PNH, thalassemia, extreme fatigue, shortness of breath upon exertion, back pain, scleral jaundice, splenectomy, cholecystectomy, and blood transfusion dependency. Concomitant medications included folic acid and ferrous sulfate. Follow-ups were received on 29MAY2008 and 04JUN2008. No new clinical information was provided to the case. Follow-up was received on 18AUG2008 from the patient. The patient received additional 600 mg Soliris infusions on 21MAY2008 and 28MAY2008, and 900 mg infusions on 03JUN2008, 17JUN2008, 01JUL2008, 15JUL2008, and 29JUL2008. On 12AUG2008, the patient missed his scheduled Soliris infusion. On 17AUG2008, the patient experienced chocolate-colored urine. Treatment consisted of drinking a lot of water, which improved the urine color. Follow-up was received on 08SEP2008 the patient. The patient's physician discontinued Soliris because his blood work was "abnormal". No further information was provided. Follow-up information was received on 10SEP2008, 16SEP2008 and 17SEP2008 from the consumer and on 16SEP2008 from a physician. The consumer received an additional 900 mg Soliris infusion on 19AUG2008. In MAY2008, the patient's baseline LDH was 250 and baseline hemoglobin level was 9. Prior to his third infusion on 21MAY2008, his LDH level decreased to 204, but then increased steadily after each subsequent Soliris infusion. In May 2008 LDH levels was 1645 prior to Soliris, 932 on 15JUL2008, 1031 on 29JUL2008, 2806 on 19AUG2008, and 2323 on 09SEP2008. Reticulocyte count was 5.3 on 01JUL2008, 11.8 on 15JUL2008, 8.4 on 29JUL2008, 10.1 on 19AUG2008, and 11.8 on 09SEP2008. Hemoglobin level was 10.7 on 15JUL2008. Flow cytometry on 29APR2008 showed monocytes with FLAER/DS14 deficiency of 95.8 percent (%) and granulocytes with FLAER/CD24 deficiency at 95.1%. Dahl-Chase type I was 70.8%, type II was 14.9% and type III was 14.5%. On 09SEP2008 late in the afternoon, the consumer's urine changed from yellow/brown to "very red". The consumer was not able to sleep and was urinating every two hours with pain in his head, muscles, and stomach when urinating. On 10SEP2008 consumer saw his physician. Treatment and outcome of the inability to sleep, urinating every two hours with pain in his head, muscles, and stomach when urinating, and very red urine were not reported. The consumer reported that his physician had "temporarily stopped Soliris" for four	Dose Omission

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		weeks of observation and if "observation not good", the physician will restart Soliris. The last dose of Soliris was on 19AUG2008. The physician was unable to confirm the events sleepy and feeling weak that occurred after the first two Soliris infusions because the patient had been under the care of another physician at the time of the events. Prednisone and an iron supplement were started as treatment. He continued to have chocolate-colored urine from time to time dependent on the amount of water that he drank. The patient was no longer transfusion dependent. His hemoglobin levels were 10.2 on 09JUL2008, and 11.7 on 10SEP2008. The physician assessed the dark colored urine as not related to Soliris. The physician was uncertain if the elevated LDH was due to Soliris or hemolysis. The consumer reported that beginning on 15SEP2008, the "mass I used to have in my neck feels like it is enlarging again and is now painful". He also reported that on 16SEP2008, he was "getting weaker, more short of breath, has joint pain, is continuing to urinate blood and is dizzy". The consumer stated that the mass was palpable by his physician in JUN2008 and in JUL2008 he underwent a "radiologic study" to "rule out cancer" and there was no cancer found. The consumer stated that the mass had been smaller while receiving Soliris. On (b) (6), the consumer reported that a urinary tract infection was diagnosed during a visit to the Emergency Room the previous night. He received treatment with a ten-day prescription of an unspecified liquid medicine. Additional medical history included coronary artery disease with angioplasty, neck mass/swelling, hemoglobinuria (black), and back pain, which was prior to splenectomy and cholecystectomy. Additional concomitant medications included prednisone, Cefadroxil (Androxy), and omeprazole (Prilosec). Follow-up information was received on 24SEP2008 from the consumer. The consumer restarted Soliris 900 mg infusions on 23SEP2008. On 16SEP2008, the consumer's LDH was elevated to 3919, reticulocytes were 16.5, hemoglobin 11.1, and hematocrit 33. The onset of the red urine event was 09SEP2008 and the event resolved on 24SEP2008. The outcomes of the elevated LDH and elevated reticulocytes were not reported.	
6200804	5/22/09	A consumer initiated treatment with intravenous (IV) Soliris. Indication, dosages, and administration dates were not provided. On an unspecified date, the consumer experienced pain in right side (midline). The pain sometimes radiated to the front and the back. Results of an unspecified ultrasound were negative. The consumer's physician had requested that the consumer go to the hospital for further tests. However, the consumer had delayed doing this due to insurance coverage issues. No further information was provided. Follow-up information was received on 15SEP2008 from the consumer and on 17SEP2008 from a nurse. This 62 year-old male initiated Soliris for paroxysmal nocturnal hemoglobinuria (PNH). He received the initial 600 mg on 21JUN2007 and received additional 600 mg infusions on 28JUN2007, 05JUL2007, and 12JUL2007. He received 900 mg infusions on 19JUL2007, 02AUG2007, 16AUG2007, 30AUG2007, 13SEP2007, 27SEP2007, 11OCT2007, 25OCT2007, 08NOV2007, 22NOV2007, 06DEC2007, 20DEC2007, 03JAN2008, 17JAN2008, 31JAN2008, 14FEB2008, 28FEB2008, 13MAR2008, 27MAR2008, 02MAY2008, 15MAY2008, 29MAY2008, 12JUN2008, 26JUN2008, 10JUL2008, 24JUL2008, 07AUG2008, 21AUG2008, 21AUG2008, and 04SEP2008. The pain was in the right hip that had started in AUG2008 and progressively worsened. Although the pain in the hip started after Soliris infusion, the consumer did not think that it was related to Soliris but believed that he might have pulled a muscle in his hip, as he had been doing construction work. <u>On 10APR2008, for an unknown reason, the patient missed a Soliris infusion.</u> The nurse confirmed that the patient experienced pain in the right hip that radiated to the leg. The patient received treatment with codeine phosphate/paracetamol (Tylenol with codeine). The right hip pain had improved. The nurse reported that the event was possibly related to Soliris. The consumer's medical history included PNH and hypertension. Concomitant medication included lisinopril.	Dose Omission

ISR NUM	RECV DATE	Narratives	Medication Error Type
7137845	12/6/10	This report was received from a nurse practitioner on 14OCT2010. A 30 year old male received treatment with intravenous eculizumab (Soliris) for paroxysmal nocturnal hemoglobinuria (PNH). He received 600 mg Soliris infusions weekly for the first four weeks beginning 29OCT2009, and switched to 900 mg every two weeks infusions on 09DEC2009. <u>The patient had missed one month of Soliris infusions during JUL2010 because of an issue with social support systems and no rides.</u> The most recent 900 mg Soliris infusion was received on 30SEP2010. The patient was hospitalized on (b) (6) for anemia and intractable vomiting and nausea. On (b) (6), a hemoglobin (Hgb) of 5.8 and platelet count of 10 were noted. He received two units of packed red blood cells (PRBC's) and two units of platelets. Treatment for the nausea and vomiting included dronabinol (Marinol), lorazepam (Ativan), metoclopramide (Reglan), ondansetron (Zofran) and prochlorperazine (Compazine). He was discharged on (b) (6). The patient was again hospitalized on (b) (6) for anemia due to the missed Soliris infusions, fever and throat infection. On (b) (6) a Hgb of 6.1 and platelet count of 2 were noted. Unspecified cultures were positive for methicillin resistant staphylococcus aureus (MRSA) however, blood and urine cultures were 'okay.' Treatment and etiology for the fever, throat infection and MRSA were not provided. The fever resolved in (b) (6). On (b) (6), a Hgb of 7.9 was noted and the anemia was considered resolved. The patient was discharged on (b) (6). The next Soliris infusion was scheduled for 14OCT2010. The reporting nurse practitioner considered the anemia, vomiting and nausea not related to Soliris. The reporting nurse practitioner did not report the causal relationships of the fever, throat infection, MRSA infection and drug dose omission to Soliris. Follow-up information was received on 22NOV2010 from a nurse practitioner. After missing Soliris infusions in JUL2010, the patient resumed infusions on 27JUL2010 and 19AUG2010. Most recent Soliris infusion was noted as 14OCT2010. On (b) (6), the patient experienced throat infection, MRSA, nausea and vomiting and was hospitalized. On (b) (6), blood cultures x 2 were collected and were negative. On (b) (6), a throat swab was positive for MRSA and Candida; a urine culture was negative. The throat was noted as the site of the MRSA infection. Fever was considered a 'symptom of infection +/- neutropenia.' Treatment for the throat infection, fever and MRSA included meropenem, vancomycin and filgrastim (Neupogen). In 2010, the throat infection, MRSA and drug dose omission were considered resolved; the nausea and vomiting remained occasionally. Medical history included PNH, aplastic anemia and iron overload. Concomitant medications included cyclosporine, Neupogen, erythropoietin (Procrit), oxycodone (Percocet and OxyContin) and deferasirox (Exjade). The nurse practitioner reported that throat infection, MRSA and drug dose omission were unrelated to Soliris therapy. Follow-up information was received on 01DEC2010 from a nurse practitioner: The patient has been neutropenic since before starting Soliris therapy. The reporter had noted fever was a symptom of the infection +/- neutropenia because the patient went into the hospital with a throat infection; fever was related to infection and the patient's body was not strong enough to fight off the infection because of the neutropenia. With the addition of treatment with filgrastim (Neupogen), neutropenia has improved but not resolved. From (b) (6) to (b) (6) the patient was hospitalized to receive an intravenous infusion of antithymocyte globulin (ATG), an immunosuppressant. ATG was given to treat aplastic anemia. Laboratory investigations included: total white blood cell count on (b) (6), (b) (6), (b) (6) and 30NOV2010 of 1.9, 0.2, 1.6 and 1.2 respectively. On 30NOV2010, hemoglobin was 7.8 g/dL and platelets were 7. The patient chose to receive ATG over a bone marrow transplant due to lack of social support (care at home) and transportation resources. The patient did well during treatment and did not experience any infection. Additional medical history included neutropenia. The reporting nurse practitioner stated ATG therapy may take six months to work, therefore, white blood cell counts may be low as a result of this therapy. Company Comment 29NOV2010: Upon receipt of follow-up, this case remains a serious (hospitalization), medically confirmed, spontaneous report of pharyngitis, staphylococcal infection, anemia, vomiting and nausea. Pharyngitis and staphylococcal infection are unlisted in the CCDS while anemia, vomiting, and nausea are listed in the Company Core Data Sheets. The non-serious event of drug dose omission and oropharyngeal candidiasis were also reported. In agreement with the HCP's opinion, the company considers the causality of the anemia, vomiting and nausea as unrelated to Soliris. The patient's medical history of aplastic anemia and neutropenia provides an alternative explanation as the cause of the events of pharyngitis and staphylococcal infection. The causality of pharyngitis and staphylococcal infection has been assessed an unrelated to Soliris. US-ALEXION-A201001305	Dose Omission

ISR NUM	RECV DATE	Narratives	Medication Error Type
7465995	5/9/11	This report was received from a consumer (patient) on 14MAY2010. A 69-year-old female initiated treatment with intravenous Soliris (eculizumab). Dates, doses, frequency and indication were not provided. During the monthly call the patient reported that she thought she had the flu. She was afebrile at the time but had complaints of nausea, slight fatigue, abdominal pain, 'MOD', back pain, slight dysphagia, shortness of breath (SOB), and slight hemoglobinuria as well as two episodes of nose bleeds. <u>On 11MAY2010, the patient missed her Soliris dose due to illness.</u> Soliris therapy was ongoing and the next infusion was scheduled for 17MAY2010. Medical history and concomitant medications were not provided.	Dose Omission
3200760	5/22/09	A 54 year-old female initiated treatment with intravenous Soliris for paroxysmal nocturnal hemoglobinuria (PNH). She received the initial 600 mg infusion on 11SEP2007 with additional 600 mg infusion on 26SEP2007, 03OCT2007 and 10OCT2007. She received the initial 900 mg infusion on 14NOV2007 with additional 900 mg infusions on 28NOV2007, 12DEC2007, 26DEC2007, 09JAN2008, 24JAN2008, 07FEB2008, 21FEB2008, 06MAR2008, 20MAR2008, 03APR2008, 17APR2008, 01MAY2008, 15MAY2008, 29MAY2008, 12JUN2008, 26JUN2008, 10JUL2008, and 24JUL2008. <u>On 20SEP2007, the consumer missed a 600 mg Soliris infusion, which was given on 26SEP2007.</u> On 25JUL2008, she started feeling sick to her stomach with body aches. The events were ongoing. The consumer's medical history included non-transfusion dependent PNH, mild MDS, pancytopenia, concentrated morning urine, blood transfusion in 1981 due to ruptured appendix, hysterectomy, fatigue, back pain, joint pain primarily in the wrists, hands, and fingers, difficulty breathing which resolves when she takes a deep breath, ileus with abdominal pain, and high antibody against hepatitis A & B. Concomitant medications included pyridoxine hydrochloride (Vitamin B6), unspecified multivitamins, iron, folic acid, prednisone, calcium, and venlafaxine (Effexor). Follow-up was received on 29AUG2008 from the consumer's physician. The consumer was receiving her Soliris infusions in an outpatient setting at the hospital. Her physician was not aware of the events. Follow-up was received on 08SEP2008 from the consumer. The events of feeling sick to her stomach and body aches started on 25SEP2007, not 25JUL2008 as previously reported. Both events resolved on 26SEP2007. On 01JUN2008, deferasirox (Exjade) was started. Follow-up information was received on 11SEP2008 from a nurse. The nurse confirmed that the patient had a single episode of body aches and feeling sick to her stomach. The patient did not receive treatment for the events. The events resolved within one day. The reporter assessed the events as not related to Soliris. Follow-up information was received on 11SEP2008 from a nurse. The nurse confirmed that the patient had a single episode of body aches and feeling sick to her stomach. The patient did not receive treatment for the events. The events resolved within one day. The reporter assessed the events as not related to Soliris. Follow-up information was received on 13OCT2008 and 17OCT2008 from the consumer and on 03NOV2008 from a nurse practitioner. The patient received an additional 900 mg Soliris infusion on 16OCT2008, rather than the scheduled infusion date of 02OCT2008 due to antithymocyte immunoglobulin (ATG)/cyclosporin treatment. The patient's initial laboratory results from the Spring/Summer of 2007 were lactate dehydrogenase (LDH) 1106, hemoglobin (HGB) 7.7, hematocrit (HCT) 23, Coombs test negative, reticulocyte count 132840, haptoglobin less than 61, HGB 8.9, HCT 26.3, and platelet count 113. Her LDH was 288 on 06MAR2008. The patient had a repeat bone marrow biopsy and consult in MAY2008. The patient developed stomachache and joint pain on 25SEP2008 after the Soliris infusion the prior day, which she felt was like a leukemia event. The events resolved within 24 hours and did not recur after subsequent infusions. ATG/Cyclosporin treatment was recommended and it was planned to continue Soliris without interruption. Cyclosporin 200 mg daily was started on 23SEP2008 and continued until 10OCT2008. ATG therapy was initiated on 26SEP2008 for four doses, two as an inpatient and two as an outpatient. Her cyclosporin level on 09OCT2008 was 900, so cyclosporin was stopped after the 10OCT2008 dose. The patient did not have the "regular flu symptoms as expected"; she "only had body aches and joint pain while on ATG". These symptoms lasted for eight hours after each ATG dose with improvement each hour. On 16OCT2008, prior to her Soliris infusion, LDH was 575, HGB 8.9, and HCT 23.6. She experienced a headache after her Soliris infusion on 16OCT2008. She self-treated with ibuprofen and "slept it off". She also experienced hemoglobinuria on the first and second voiding on 16OCT2008. These were the first episodes of hemoglobinuria since initiating Soliris on 11SEP2007. The headache resolved on 17OCT2008, but she "did not feel right" on 17OCT2008. She felt run down and foggy. Additional medical history included transfusions since summer of 2007 and ATG/cyclosporin treatment between 23SEP2008 and 10OCT2008 with side effects of body aches and joint pain for eight hours after each dose of ATG. The nurse practitioner assessed the stomachache and joint pain as not related to Soliris.	Dose Omission

ISR NUM	RECV DATE	Narratives	Medication Error Type
6894638	8/2/10	This report was received from a consumer (patient's friend) on 04MAY2010. An 86-year-old male patient initiated treatment with intravenous Soliris (eculizumab) for an unspecified indication. He received his first dose (dosage unspecified) of Soliris on 02APR2010. On 28APR2010, the patient moved back to (b) (6) from (b) (6). <u>The patient's friend reported that the patient did not get his fifth dose of Soliris in (b) (6) as the (b) (6) doctor did not write for the dose to be given in week five; rather the physician wrote for week six. Over the weekend, the patient developed a cold, cough and dizziness.</u> He went to the emergency room and was admitted on (b) (6). Additionally, while hospitalized, his hemoglobin went down to 6 and he was given three units of blood. The friend stated that there was no evidence of pneumonia or bronchitis, but he was being treated with antibiotics anyway. At the time of report, the patient remained hospitalized, with hopes of being possibly discharged on (b) (6). The outcomes of the events were not reported. No additional information was available. Medical history and concomitant medications were not reported. Follow-up information was received on 29JUN2010 from a consumer. The patient received his fifth dose of Soliris on 07MAY2010. The patient was 'o.k. now' and had no cough, no cold and no dizziness. Follow-up information was received on 07JUL2010 from a nurse. Per the hospital discharge summary, the patient was hospitalized on (b) (6) for anemia secondary to paroxysmal nocturnal hemoglobinuria (PNH) with dizziness and lightheadedness. He also had a cough with some greenish sputum and his urine was dark colored. On admission, his temperature was 99.2, white blood cell count (WBC) was 5.7, hemoglobin was 7.7, and hematocrit was 22.2. A computerized tomography (CT) scan of the head showed some cerebral atrophy and evidence of sinusitis involving the ethmoid region. He received three units of packed cells and on the morning of (b) (6) he was feeling better and was afebrile. He also received moxifloxacin (Avelox) and fluticasone (Flonase) for the sinusitis with meclizine (Antivert) as needed for dizziness. On (b) (6), his aspartate aminotransferase (AST) was slightly elevated at 57 and total bilirubin was elevated at 2.6. On (b) (6), he received one more unit of red cells. On (b) (6), his potassium was decreased to 2.5 and he was treated with potassium replacement. Also on (b) (6), his AST was down to 47 and total bilirubin was down to 1.7. On (b) (6) his WBC was down to 3.0 and he had thrombocytopenia with a platelet count decreased to 66000. The physician was unsure if this was related to PNH or to Soliris treatment. On (b) (6), the patient's WBC was 3.0, hematocrit was 30.1, hemoglobin 10.4, and platelet count 66000. His potassium level was increased to 3.0, blood urea nitrogen was down to 19 from 28, and serum creatinine was 1.2. The patient was discharged home on (b) (6). Medical history included PNH, hypertension, prostate cancer, retinal detachment, gastroesophageal reflux disease, and chronic insomnia. Concomitant medications included bicalutamide (Casodex), perindopril/erbumine (Aceon), amlodipine (Norvasc), olopatadine hydrochloride (Patanol), folic acid, pyridoxine, zolpidem tartrate (Ambien), lansoprazole (Prevacid), cyanocobalamin (Vitamin B12), calcium, and laxatives. Follow-up information was received on 22JUL2010 from a medical secretary. The patient received his fourth infusion of 600 mg Soliris on 30APR2010 and his fifth infusion at 900 mg on 07MAY2010. The most recent 900 mg infusion was received on 23JUN2010. The medical secretary read from the physician's notes. On 28MAY2010, a WBC of 4.9, potassium of 3.6 and lactate dehydrogenase of 256 were noted. The patient was last seen on 23JUN2010 and he has cancelled all appointments since then but the reporter did not know why. Company Comment 22JUL2010: Upon receiving the last follow-up information, this case remains a serious (hospitalization), medically confirmed solicited report of acute sinusitis with symptoms of cough and green sputum, and anemia with symptoms of dizziness and lightheadedness. Acute sinusitis is unlisted in Company Core Data Sheets, while anemia is listed. The rest of events were also reported as non-serious events. The company considers the causality of acute sinusitis as possible related to Soliris due to the existing temporal relationship, while anemia as unlikely unrelated to the product citing patient's underlying disease PNH. US-ALEXION-A201000506	Dose Omission
6547874	1/24/10	This report was received from a consumer on 10NOV2009. A 26-year-old male patient initiated treatment with intravenous Soliris (eculizumab) for treatment of paroxysmal nocturnal hemoglobinuria (PNH), date and dose information unspecified. The most recent infusion was on 02NOV2009. <u>The patient reported that he missed his scheduled infusion of Soliris on 23OCT2009. Instead he received it on 02NOV2009,</u> and now he is feeling cold and had a return of dark urine. No other information was available. Medical history included PNH and prior urine discoloration. Concomitant medication was not reported. Follow-up information was received on 17NOV2009 from a physician. The physician stated that the patient had been on Soliris for three to four months and was doing well. In NOV2009, the events of feeling cold and dark urine resolved, and were considered symptoms of hemoglobinuria. The physician further stated that he did not know why the patient had symptoms, but they were not related to Soliris. The physician also noted that the patient missed a scheduled infusion because he could not get to the clinic. Therapy with Soliris 900 mg every two weeks remained ongoing. Concomitant medications included folic acid and iron. The reporting physician considered the events of feeling cold and dark urine not related to Soliris therapy.	Dose Omission

ISR NUM	RECV DATE	Narratives	Medication Error Type
7044854	10/14/10	This report was received from a nurse on 23SEP2010. A 39 year old male patient received treatment with intravenous eculizumab (Soliris) for paroxysmal nocturnal hemoglobinuria (PNH). Dates and doses of treatment were not provided. At the time of report, the patient's 'line was infected.' Soliris continued. Medical history included PNH. Concomitant medications were not provided. The reporting nurse did not report the causal relationship of the catheter infection to Soliris treatment. Follow-up information was received on 27SEP2010 from a physician. The patient developed a methicillin resistant staphylococcus aureus (MRSA) infection however, the source of the infection was unknown. <u>In the recent past, he also missed multiple Soliris doses due to poor intravenous (IV) access.</u> Soliris continued. The reporting physician did not report the causal relationship of the MRSA infection, missed multiple Soliris doses and poor IV access to Soliris treatment. Follow-up information was received on 04OCT2010 from a nurse. The patient's catheter dressing and needle had not been changed in three weeks. The patient currently has no IV access. No other information was available. The reporting nurse did not report the causal relationship of the catheter infection, MRSA infection, missed multiple Soliris doses and poor IV access to Soliris treatment. Follow-up information was received on 04OCT2010 from a physician: Most recent Soliris infusion was 900 mg on 14SEP2010. The patient missed his 21SEP2010 Soliris dose. The physician reported the porter catheter in the patient's groin was infected with MRSA. The MRSA infection has been occurring off and on for the past three years, since 2007. The patient is taking vancomycin 1 gram every 12 hours for the MRSA infection. An ultrasound was supposed to be taken of the groin but it has not been done. A new line has not been placed yet as the physician is waiting for a vascular surgeon to see the patient. The physician reported the patient has had a poor IV access prior to starting Soliris therapy. Medical history also includes diabetes, anger management, upper clot in chest, hit a wall and got a closed head injury and poor IV access. Concomitant medications were not provided. The reporting physician considered the porter catheter in groin infection, MRSA infection and missed Soliris doses as not related to Soliris therapy. He stated it was due to the patient playing or fiddling with the line. Also the patient is colonized with MRSA because he stays in an institution. Company comment 04OCT2010: This case is a serious (medically significant), medically confirmed spontaneous report of device related MRSA infection (coded to staphylococcal infection and device related infection). The event of device related MRSA infection is unlisted in the Company Core Data Sheets. The missed multiple Soliris doses were also reported as a non-serious event. In agreement with the HCP's opinion, the company considered the causality of the device related MRSA infection as unrelated to Soliris, and related to the patient playing or fiddling with the line and an institutional environment. US-Alexion-A201001230	Dose Omission
6200738	5/22/09	A 25-year-old male patient initiated treatment with intravenous Soliris for paroxysmal nocturnal hemoglobinuria (PNH). He received the initial 600 mg infusion on 01MAY2008. On 02MAY2008, after the first infusion, the consumer experienced diarrhea. On 03MAY2008, the diarrhea resolved without treatment. Medical history included PNH and hypertension. Concomitant medications included hydrochlorothiazide. Follow-up information was received on 08JUL2008 from a pharmacy employee. <u>The patient missed his Soliris dose on 26JUN2008.</u> The Soliris 900 mg infusion was received on 03JUL2008. Follow-up information was received on 09JUL2008 from a nurse. The patient received 600 mg Soliris infusions on 08MAY2008, 15MAY2008, 22MAY2008 and 900 mg infusions on 29MAY2008, 12JUN2008, and 03JUL2008. On 26JUN2008, the patient missed his scheduled Soliris infusion due to a fever of 102.3 degrees Fahrenheit, chills, heart rate of 112, and a sore throat with purulent drainage. He received treatment with ciprofloxacin (Cipro). All events resolved in JUL2008. The missed Soliris dose was administered on 03JUL2008.	Dose Omission

SR NUM	RECV DATE	Narratives	Medication Error Type
200408	5/22/09	A 43 year-old female initiated treatment with intravenous eculizumab (Soliris) 600 mg on 26APR2007, for paroxysmal nocturnal hemoglobinuria (PNH). She received additional infusions of 600 mg Soliris on 03MAY2007, 10MAY2007, 17MAY2007 and 24MAY2007 and 900 mg infusions on 06JUN2007 and 20JUN2007. Prior to each Soliris treatment, the patient received paracetamol (Tylenol) and ondansetron (Zofran). On 11MAY2007, the patient experienced a light headache. She received paracetamol (Tylenol) with relief. On 21JUN2007, the patient felt tired and was noted to have a decreased hematocrit. Test results on 21JUN2007 included a hematocrit of 18.9, white blood cell count of 3.2, hemoglobin of 6.5 and platelet count of 91. It was noted that her hematocrit was 23.9 on 06JUN2007. She had no signs of infection. On 22JUN2007, the patient received three units of red blood cells. The tiredness resolved on 22JUN2007. The outcome of decreased hematocrit was not reported. The patient's medical history included PNH, kidney failure, an allergy to Levaquin and other unspecified antibiotics, low white blood cell level, no history of infection, and blood transfusions approximately every month with her last blood transfusion in APR2007. It was noted that since treatment with Soliris the patient is able to go longer intervals prior to transfusion. Concomitant medications included paracetamol (Tylenol), ondansetron (Zofran), deferasirox (Exjade), and heparin fraction (Lovenox). Additional information was received on 18FEB2008. The patient received additional 900 mg Soliris infusions on 06JUL2007, 19JUL2007, 02AUG2007, 16AUG2007, 30AUG2007, 13SEP2007, 27SEP2007, 11OCT2007, 25OCT2007, 08NOV2007, 19NOV2007, 06DEC2007, 20DEC2007, 03JAN2008, 17JAN2008, 31JAN2008, and 17FEB2007. On 16FEB2008, 16 days after her 23rd Soliris infusion, the patient stated that she experienced hemolysis characterized by hemoglobinuria, shortness of breath, fatigue, abdominal pain, and vomiting. <u>The patient's infusion was due on 14FEB2008, but was delayed for unknown reasons until 17FEB2008.</u> On 18FEB2008, the hemolysis resolved. The physician was unable to confirm the hemolytic episode, but did confirm that the Soliris infusion was late. Laboratory test results were pending. Follow-up was received on 25FEB2008. The patient experienced her usual symptoms prior to the Soliris infusion that was delayed until 17FEB2008 due to a problem with the pharmacy. On 17FEB2008 prior to Soliris infusion the patient's hemoglobin level was 9.5, hematocrit was 26.9, mean cell volume was 102.7, mean cell hemoglobin was 36, white cell count was 3.5, and platelet count was 70000. These values were within the normal range for this patient. The physician assessed the causality of the hemolysis, fatigue, and decreased hematocrit to be related to the delayed Soliris infusion. The physician assessed the headache to be related to Soliris.	Dose Omission
6200765	5/22/09	A 32-year-old male initiated treatment with intravenous Soliris for paroxysmal nocturnal hemoglobinuria (PNH). He received the initial 600 mg infusion on 11FEB2008 with additional infusions on 18FEB2008, 25FEB2008 and 03MAR2008, and 900 mg infusions on 10MAR2008, 24MAR2008, 07APR2008, 21APR2008, 05MAY2008, 19MAY2008 and 02JUN2008. <u>The Soliris infusions were placed on hold for an unspecified reason,</u> and then restarted on 15JUL2008 due to increased lactate dehydrogenase (LDH) level (results not available). In FEB2008, after the first Soliris infusion, the consumer experienced two episodes of nausea. Treatment was unknown. The nausea resolved in FEB2008. The consumer's medical history included PNH, cerebral palsy, and seizure disorder. Concomitant medications included levetiracetam (Keppra) and lamotrigine (Lamictal).	Dose Omission
6200646	5/22/09	A 67 year-old female initiated treatment with intravenous (IV) Soliris for paroxysmal nocturnal hemoglobinuria (PNH). She received the initial 600 mg infusion on 08JUN2007. Additional infusion dates and dosages were not provided. On (b) (6), <u>the patient was hospitalized for treatment of ketoacidosis diabetic crisis. She missed the (b) (6) Soliris infusion.</u> Treatment was unknown. The diabetic crisis was considered resolved in (b) (6). The patient was discharged on (b) (6). She received a 900 mg Soliris infusion on 28APR2008. The patient's medical history included PNH, diabetes, and chronic renal failure. Concomitant medications were not provided. Follow-up was received on 13MAY2008 by the physician. The physician considered the ketoacidosis diabetic crisis not related to Soliris.	Dose Omission
200773	5/22/09	A 42-year-old female patient initiated treatment with intravenous (IV) Soliris for paroxysmal nocturnal hemoglobinuria (PNH). She received the initial 600 mg infusion on 07JUN2007 with additional 600 mg infusions on 14JUN2007, 21JUN2007, 28JUN2007, and 900 mg infusions on 05JUL2007, 19JUL2007, 02AUG2007, 16AUG2007, 30AUG2007, 13SEP2007, 27SEP2007, 11OCT2007, 25OCT2007, 22NOV2007, 06DEC2007, and 20DEC2007. <u>Due to insurance issues, the 08NOV2007, 03JAN2008 and 17JAN2008 infusions were missed and the patient received a reinduction infusion of 600 mg on 28JAN2008.</u> On 25JAN2008, after the 16th Soliris infusion, the patient experienced dark bloody urine. On 28JAN2008, blood work prior to Soliris infusion showed an elevated bilirubin of 1.9, white blood cell (WBC) count of 3.1, red blood cell (RBC) count of 2.6, hemoglobin of 9.3, hematocrit of 26.5, and platelet count of 212 000. On 29JAN2008, additional blood work revealed a lactate dehydrogenase (LDH) of 2160. On 31JAN2008, the patient experienced headache and increased heart rate. On (b) (6), she	Dose Omission

ISR NUM	RECV DATE	Narratives	Medication Error Type
		was hospitalized with nausea, vomiting, and a temperature of 102 degrees; admitting diagnosis was pancytopenia and pyrexia. The nausea and vomiting resolved on the same day. On (b) (6), hemoglobin level was 5.4 and results of blood cultures were pending. Treatment included oral prednisone 20 mg twice a day, intravenous ceftriaxone (Rocephin) 100 mg every 12 hours and paracetamol (Tylenol) for the fever. On (b) (6), a urine test indicated an elevated urobilinogen of 8.0. The urine was clear and yellow, with no sign of blood. Follow-up blood work on (b) (6), indicated an improved LDH of 311. As of (b) (6), the patient was afebrile, but experiencing some lightheadedness. The elevated LDH level improved. The dark blood in urine resolved on (b) (6). Outcome of pancytopenia, increased heart rate, headache, elevated bilirubin, and elevated urobilinogen was unknown. Lightheadedness was ongoing. At the time of reporting, the patient remained hospitalized. The patient's medical history included PNH, gastroesophageal reflux disease (GERD), and hemoglobinuria (last episode before Soliris therapy). Concomitant medication included ranitidine hydrochloride (Zantac). Follow-ups were received on 12FEB2008 and 13FEB2008. The patient received an additional Soliris 600 mg infusion on 12FEB2008. The patient reported to her physician that she experienced hematuria prior to hospital admission. The physician confirmed the nausea, vomiting, and that the patient was admitted for pancytopenia and fever but could not confirm the increased heart rate, headache, and elevated bilirubin, as the events happened prior to hospitalization. Elevated urobilinogen and lightheadedness not confirmed either. The outcome of the events was not provided. Hospital discharge date was unknown. Laboratory and blood culture results, and hospital discharge summary were not available to the physician. The physician could not assess the causal relationship of the events to Soliris. Additional events were also reported by the patient. Since an unspecified date in 2008, the patient experienced feeling tired, chest heaviness, shortness of breath upon waking, and feeling like something was stuck in her throat. In addition, on 12FEB2008, after the second Soliris reinduction infusion, the patient experienced an itchy rash to the lower abdomen and down both legs, as well as seven itchy bumps to both hands. The itchy rash was treated with IV diphenhydramine hydrochloride (Benadryl). On 12FEB2008, the patient hemoglobin level was 8.6. The itchy rash and the hand bumps resolved on 13FEB2008. Outcome of the other events was unknown. Follow-up was received on 14AUG2008 from the consumer. The patient received 600 mg Soliris infusions (re-induction) on 19FEB2008 and 21FEB2008. She received 900 mg infusions on 28FEB2008, 13MAR2008, 27MAR2008, 15APR2008, 29APR2008, 13MAY2008, 27MAY2008, 10JUN2008, 24JUN2008, 08JUL2008, 22JUL2008, and 05AUG2008. On 12AUG2008, seven days after the last Soliris infusion, the patient's hemoglobin level dropped to 8.4. She received two units of packed red blood cells on 13AUG2008. Outcome was unknown. Medical history included last prior blood transfusion received in (b) (6).	
6178617	5/4/09	A 35-year-old female initiated treatment with intravenous (IV) Soliris for paroxysmal nocturnal hemoglobinuria (PNH). She received the initial 600 mg infusion on 02NOV2007, and her last 900 mg infusion on 12MAR2008. The patient had a history of elevated blood glucose since 2003; her normal levels were between 125 to 130 mg/dl. On 13MAR2008, the patient blood glucose level was 233 mg/dl. On 15MAR2008, glipizide 5 mg daily was started. On 20MAR2008, the patient's fasting blood glucose was 116 mg/dl. As per the patient, her physician specified that the increased glucose level was due to chronic prednisone use. The patient's medical history included PNH, elevated blood glucose, and a family history of diabetes. Concomitant medications included iron, folic acid, prednisone, and pantoprazole. Follow-up was received on 01MAY2008. The patient received additional 900 mg Soliris infusions on 25MAR2008, 08APR2008, and 22APR2008. In APR2008, the patient experienced dizziness, which occurred for four to five seconds when walking and resolved upon sitting down. On an unknown date, the patient went to the emergency room (ER) for the dizziness; her blood pressure was 99/55 (her usual blood pressure was 120/80). Hemoglobin level was 10.6, which was "good". The patient was not admitted and it was unknown if any treatment was provided. On an unspecified date in APR2008, prednisone was decreased to 5 mg every other day due to low blood pressure and increased blood glucose levels. On 17APR2008, prednisone dosage was increased back to 5 mg every day. Also in APR2008, the patient experienced vaginal bleeding, which was not her period. The dizziness and vaginal bleeding were ongoing. Outcome of low blood pressure was unknown. In APR2008, the patient's fasting blood glucose was between 109 and 137. Follow-up was received on 23MAY2008 from a pharmacist. On (b) (6) the patient presented to the emergency room (ER) with left-sided chest pain for four days, nausea, dizziness, and pain at the back of her neck. Her blood pressure was 137/65 and her pulse rate was 85 beats per minute. An electrocardiogram (ECG) showed normal sinus rhythm and no significant change from a previous ECG on 29APR2007. Additional blood pressure readings while in the ER were 99/57 with pulse rate of 60 beats per minute and 102/60 with pulse rate of 63 beats per minute. The chest pain was thought to be chest wall pain and not cardiac related. A D-Dimer was within normal limits at 0.23 on (b) (6). The patient was released from the ER with treatment of ibuprofen 600 mg every six hours as needed. The discharge diagnosis was non-cardiac chest pain. The chest pain, nausea, dizziness, pain at the back of the neck, and hypotension were resolved in (b) (6). The pharmacist assessed the chest pain as not related to Soliris	Dose Omission

SR NUM	RCV DATE	Narratives	Medication Error Type
		therapy. Follow-up was received on 05SEP2008 from the patient. The patient was still receiving Soliris. She had experienced a headache every day during the previous week. In addition, she felt a little nauseated and had a backache. She denied any fever. The patient was advised to report the events to her physician. Follow-up information was received on 11SEP2008 and 17SEP2008 from a pharmacist. The patient received an additional 900 mg Soliris infusion on 02SEP2008. <u>A few doses of Soliris were missed due to the patient traveling to Mexico on occasion.</u> The reporter did not have the exact dates that the infusions were missed and no events were experienced during that time. The patient did not report the headache or the backache to the pharmacist. The nausea had resolved. Soliris therapy was ongoing. Causal relationship to Soliris was unknown. Follow-up information was received on 27MAR2009 from a nurse. The patient had experienced head and back pain prior to Soliris initiation. No treatment was provided and the events were ongoing intermittently. As of 27MAR2009, due to the patient being six to seven week pregnant, Soliris therapy was on hold until the third trimester of the pregnancy. The nurse considered the head pain and the back pain not related to Soliris therapy.	
7467875	5/9/11	This report was received from a consumer on 18JAN2011. A 75 year-old male initiated treatment with intravenous Soliris (eculizumab) for paroxysmal nocturnal hemoglobinuria (PNH). Soliris start date and dosing details were not provided. <u>The patient missed his last dose scheduled (b) (6) due to hospitalization. A friend of the patient reported that on (b) (6), the patient was admitted to the hospital after taking too many pain meds.</u> He was unable to respond appropriately or to walk. The patient himself reported that he was not quite sure why he was re-admitted; he noted he has been receiving dialysis three times per week since the (b) (6) hospitalization (Ref. case # A201001675). He noted he has been on and off dialysis for several years now secondary to kidney disease. The patient further reported he was scheduled to receive his Soliris infusion on (b) (6), and then be discharged to a rehab facility for approximately one month while he recovers. The patient remains unable to work at this time, although he has tried to use the walker. He did state that he thinks he has improved since admission. No additional information was provided. Medical history included PNH, kidney disease, and dialysis. Concomitant medications included an unspecified pain medication. Company Comment 18JAN2011: This is a serious, medically unconfirmed, solicited report of Overdose, Mental impairment, and Abasia (all Hospitalization). Mental impairment and Abasia are considered symptoms of the Overdose. Overdose is unlisted in the CCDS. Because the patient overdosed on a pain medication and not Soliris, the company considers the event of Overdose as unrelated to Soliris therapy. US-Alexion-A201100079	Dose Omission
6677860	4/12/10	This report was received from a buyer on 17MAR2010. A 59 year-old female initiated treatment with intravenous Soliris (eculizumab) for paroxysmal nocturnal hemoglobinuria (PNH). She received 600 mg Soliris infusions weekly for four weeks from 16MAR2009 until APR2009, and switched to 900 mg every two weeks on an unspecified date in APR2009. <u>On (b) (6) the buyer stated that the patient had recently been in the hospital and had missed her last two Soliris infusions.</u> Soliris therapy was ongoing. No additional information was provided. Medical history included PNH, streptococcal pneumonia in NOV2008, deep vein thrombosis (DVTs), atrial fibrillation, portal vein thrombosis and diabetes. Concomitant medication included warfarin sodium (Coumadin), lisinopril, sotalol, amlodipine besylate, escitalopram oxalate, acetylsalicylic acid (Aspirin), metformin, folic acid, insulin glargine, and insulin aspart. Follow-up information was received on 23MAR2010 from a patient. The patient missed Soliris infusions on (b) (6) and (b) (6) due to hospitalization for an unknown diagnosis. On 22MAR2010, the patient resumed her usual Soliris dosing schedule of 900 mg every 14 days. On 23MAR2010, during a follow-up call following a reintroduction of Soliris infusions, the patient reported cold symptoms and a sore throat. Audible coughing was also heard by her case manager. At the time of reporting, the patient had not reported the symptoms to her physician. No additional information was provided. Company Comment 17& 23MAR2010: This is a serious (hospitalization), not medically confirmed, spontaneous consumer report of unevaluable event. The event is unlisted in Company Core Data Sheets. The rest of the events were also reported as non-serious events. The case has insufficient details for a meaningful causality assessment. US-ALEXION-A201000320	Dose Omission

ISR NUM	RECV DATE	Narratives	Medication Error Type
6944749	8/27/10	This report was received from a physician and a nurse on 29JAN2010. A 32 year-old female initiated treatment with intravenous Soliris (eculizumab). Soliris indication, dates, and dosages were not provided. The patient was pregnant. No additional information was provided. Medical history and concomitant medications were not provided. Follow-up information was received on 09FEB2010 from a registered nurse. The patient received 600 mg Soliris infusions weekly for the first four weeks from 17NOV2009 until 08DEC2009, and switched to 900 mg infusions on 23DEC2009. <u>The first 900 mg infusion was on 23DEC2009 because the patient accidentally skipped a week. Also, a Soliris infusion was missed due to the (b) (6) hospitalization. The most recent 900 mg Soliris infusions were received on 19JAN2010 and (b) (6).</u> The pregnancy was confirmed and ongoing. The patient had been referred to an institution for an abortion. The date of the patient's last menstrual period was unknown. In (b) (6), the patient was hospitalized when her 'counts were down' due to pregnancy. The patient was hospitalized for one week and discharged on (b) (6). Medical history included paroxysmal nocturnal hemoglobinuria (PNH). Follow-up information was received on 11FEB2010 from a physician. On 18JAN2010 the following lab values were noted: white blood cell (WBC) count $2.5 \times 10^3/\text{ul}$; red blood cell (RBC) count $2.91 \times 10^6/\text{ul}$; hemoglobin 9.7 g/dl; hematocrit 29.3%; platelets $80 \times 10^3/\text{ul}$; absolute neutrophils $0.9 \times 10^3/\text{ul}$, creatinine 0.47 mg/dl and blood urea nitrogen (BUN)/creatinine ratio 28. On (b) (6) the following lab values were noted: creatinine 0.5 mg/dl; calcium 8.1 mg/dl, total bilirubin 1.8 mg/dl; total protein 5.7 g/dl, albumin 2.8 g/dl; WBC $1.6 \times 10^3/\text{ul}$; $2.44 \times 10^6/\text{ul}$; hemoglobin 8.6 g/dl; hematocrit 23.5% and platelets $40 \times 10^3/\text{ul}$. Follow-up information was received on 16FEB2010 from a registered nurse. The patient decided not to terminate the pregnancy. Follow-up information was received on 24FEB2010 and 25FEB2010 from a registered nurse. The most recent 900 mg Soliris infusion was received on 16FEB2010. At the time of report, the patient was 12-14 weeks pregnant. The patient's due date was not known at this time. Baseline laboratory results from 04NOV2008 included WBC $2.4 \times 10^3/\text{ul}$, RBC $3.09 \times 10^6/\text{ul}$, hemoglobin 10.0 g/dl, hematocrit 29.5% and platelet count $20 \times 10^3/\text{ul}$. A discharge summary was received and provided details surrounding the (b) (6) hospitalization. The patient was hospitalized on (b) (6) with symptomatic anemia and pancytopenia secondary to paroxysmal nocturnal hemoglobinuria. She presented with complaints of generalized weakness and fatigue for one week as well as headache, and several episodes of nausea and vomiting. On admission, laboratory results included hemoglobin of 6.2, WBC of 1600 and platelet count of 47,000. The patient was admitted to a telemetry unit and transfused with two units of packed red blood cells and her hemoglobin improved to 8.6. Another unit of packed red blood cells was transfused after this. On day 2 of hospitalization, the patient was ambulatory and her fatigue and generalized weakness had improved. The patient continued to have intermittent vomiting about once a day, which was relieved by antiemetics. A computerized tomogram (CT) scan of the head revealed no acute intracranial abnormality. An ultrasound of the abdomen revealed a viable fetus with an estimated gestation equal to 10 weeks and 4 days. The patient was stable and discharged to home on (b) (6). Discharge diagnoses included symptomatic anemia secondary to paroxysmal nocturnal hemoglobinuria, PNH, pancytopenia secondary to PNH, mild nausea and vomiting (likely secondary to pregnancy), and intrauterine pregnancy. Discharge medication included ondansetron (Zofran). The next Soliris infusion was scheduled for 02MAR2010. Additional medical history included cerebrovascular accident, deafness, muteness, hyperemesis in previous pregnancies and migraines. The patient was not receiving any concomitant medications. The nurse considered the event of 'counts were down' as not related to Soliris but related to pregnancy. Follow-up information was received on 07MAY2010 from a healthcare professional (medical assistant). On 26MAR2010, the medical assistant reported that the patient experienced decreased hemoglobin (value unspecified). On 14APR2010, her hemoglobin level was 7.9 (normal range: 11.5-16), and at a different laboratory on 19APR2010, her hemoglobin level was 10.4 (normal range: 12-16). The decreased hemoglobin was considered to be improved at the time of reporting. The patient's pregnancy remained ongoing, with an estimated due date of 03SEP2010. It was not known whether the patient was using birth control; however the pregnancy was not planned. Additional medical history included aplastic anemia. The patient had no prior history of transfusion dependence. The medical assistant considered the decreased hemoglobin unrelated to Soliris therapy. Follow-up information was received on 03JUN2010 from a healthcare professional (nurse). Most recent Soliris infusion was noted to be 900 mg on 21MAY2010. On 26MAR2010, the patient's hemoglobin was 6.8 and her hematocrit was 20.9. On 14APR2010, hemoglobin was 7.9, hematocrit was 23.9 and red blood cell count was 2.4. No treatment was provided. The nurse could not provide a causality relationship for the events of low creatinine, increased BUN/creatinine ratio, low calcium, increased total bilirubin, decreased albumin and headache and Soliris therapy. Follow-up information was received from a physician on 26MAY2010 and 01JUN2010. No new clinical information was provided. Medical history included pregnancy with loss of fetus after stroke, but prior to Soliris therapy. He confirmed that the patient was in her second trimester. Follow-up information was received on 03JUN2010 from a company representative (PV Analyst). Medical history included stroke on (b) (6), followed by an aborted pregnancy sometime thereafter prior to Soliris. Follow-up information was received	Dose Omission

SR NUM	RECV DATE	Narratives	Medication Error Type
		on 15JUN2010 from the patient's mother-in-law. The patient received two units of packed red blood cells (PRBCs) and a platelet transfusion at the end of (b) (6). She is now in her third trimester and her due date is 04SEP2010. Follow-up information was received on 18AUG2010 from a consumer (patient's mother-in-law). Most recent infusion of Soliris was received on 13AUG2010. On (b) (6), the patient delivered a baby girl via cesarian section. The baby weighed five pounds 12 ounces, and both baby and mother were reported as doing well. Company Comment 18AUG2010: Upon receipt of last follow-up from the consumer, the case maintains a serious (hospitalization), medically confirmed, spontaneous report of pancytopenia and symptomatic anemia with symptoms of weakness and fatigue. Pancytopenia is unlisted in Company Core Data Sheets, whereas anemia is listed. Other reported events are non serious. In agreement with reporting Healthcare Provider the company considers pancytopenia and symptomatic anemia not related to Soliris, but to underlying PNH. US-ALEXION-A201000110	
6200827	5/22/09	A 65 year-old male initiated treatment with intravenous Soliris for paroxysmal nocturnal hemoglobinuria (PNH). He received the initial 600 mg infusion on 16OCT2007 with additional infusions on 23OCT2007, 30OCT2007 and 06NOV2007, and 900 mg infusions on 13NOV2007, 05DEC2007, 19DEC2007, 02JAN2008, 16JAN2008, 30JAN2008, 13FEB2008, 26FEB2008, 11MAR2008, 25MAR2008, 08APR2008 and 22APR2008. On an unknown date, blood work revealed abnormal potassium and phosphate levels. Treatment included sevelamer (Renagel) 800 mg, two tablets with each meal. Also on an unknown date, a computerized tomography (CT) scan detected a kidney mass. On 27NOV2007, the patient did not receive his scheduled infusion due to poor venous access. A peripherally inserted central catheter (PICC) was placed and the patient received his infusion on 05DEC2007. In (b) (6), the patient underwent a right nephrectomy. The kidney mass was confirmed to be cancerous. On 28APR2008, the patient developed a red sore throat and sinusitis characterized by head congestion and yellow/green blood tinged sputum. Treatment for the sinusitis and red sore throat consisted of azithromycin (Z-Pack), which only provided some relief for the red sore throat. The cancerous kidney mass was considered resolved in (b) (6). The outcome of abnormal potassium and phosphate levels was unknown. The red sore throat improved. The sinusitis was ongoing. The patient's medical history included PNH, sinusitis with head congestion, and dialysis twice weekly for three hours. Concomitant medications were not provided. Follow-up was received on 07AUG2008 from the consumer. The consumer received additional 900 mg Soliris infusions on 06MAY2008, 20MAY2008, 03JUN2008, 17JUN2008, 01JUL2008, and 15JUL2008. On 27JUL2008, the consumer experienced a "yeast fungal infection in the entire body including both eyes". No treatment was initiated for the event and the event was ongoing. <u>The consumer missed his 29JUL2008 Soliris infusion. It was scheduled for 12AUG2008. Follow-up information was received on 26AUG2008 from the consumer. The consumer reported that a yeast infection in his blood and both eyes was diagnosed by a blood culture on 31JUL2008. Treatment was initiated with voriconazole (Vfend). Follow-up information was received on 19SEP2008 from the consumer. On (b) (6), the consumer underwent a left eye surgery to help clear up the fungal infection in his eye. The same procedure was scheduled for (b) (6) for his right eye. The consumer was not treated with Soliris at the time of this report.</u>	Dose Omission
6200785	5/22/09	A 53 year-old female initiated treatment with intravenous Soliris for paroxysmal nocturnal hemoglobinuria (PNH). She received the initial 600 mg infusion on 21MAR2008 with additional 600 mg infusions on 28MAR2008, 04APR2008 and 11APR2008 and 900 mg infusions on 18APR2008, 02MAY2008, 16MAY2008, 30MAY2008, 13JUN2008, 27JUN2008, and 16JUL2008. On 11JUL2008, <u>the consumer experienced low blood count, and her scheduled Soliris infusion was held that day.</u> On (b) (6), she experienced hemoglobinuria leading to hospitalization. Treatment consisted of an unspecified blood transfusion. On (b) (6) the consumer was given the missed Soliris dose, her urine cleared up, and she was discharged home. On unknown dates, her hemoglobin levels were 5, 6 and 7. All adverse events resolved. The consumers' medical history included PNH. There were no concomitant medications. Follow-up information was received on 25AUG2008 from a physician. The physician confirmed the hemoglobinuria and the missed Soliris dose (11JUL2008). The physician assessed the hemoglobinuria as unrelated to Soliris and related to the missed dose.	Dose Omission

ISR NUM	RECV DATE	Narratives	Medication Error Type
6200434	5/22/09	A 32-year-old male initiated treatment with intravenous (IV) Soliris for paroxysmal nocturnal hemoglobinuria (PNH). He received the initial 600 mg infusion on 06FEB2008 with additional infusions on 13FEB2008 and 05MAR2008. Prior to starting Soliris, the patient had hypertension due to PNH, which was treated with diet changes and no medication. His usual blood pressure was 130/80. After starting Soliris, the patient experienced worsened hypertension. On 19FEB2008, his blood pressure was 170/80. Treatment included hydrochlorothiazide. On an unspecified date in FEB2008, his blood pressure was 153/80. In addition, since FEB2008, the patient experienced decreased energy and depression. The patient believed that the depression was probably due to the fact that he could not find employment. The blood pressure improved and was reportedly "almost normal" in MAR2008. The decreased energy and depression were ongoing. The patient's medical history included PNH and hypertension. Concomitant medications included tocopherol (Vitamin E), chondroitin, glucosamine, and milk thistle. Follow-up was received on 21MAR2008. The patient received an additional 900 mg infusion of Soliris on 20MAR2008. On an unspecified date in MAR2008, the patient developed a cold. No treatment was prescribed. The outcome of the cold was unknown. The reporter indicated that the event cold was not related to Soliris. Follow-up was received on 04AUG2008 from the patient. The patient received additional Soliris infusions on 26MAR2008, 09APR2008, 19APR2008, 03MAY2008, 17MAY2008, 31MAY2008, 04JUN2008, and 28JUN2008. <u>The 19JUL2008 Soliris infusion was not received due to "mix-up with the infusion company". The Soliris infusion was scheduled on 05AUG2008. In JUL2008, the patient experienced pain and swelling of the left leg. No treatment was rendered. The events were ongoing.</u>	Dose Omission
6548026	1/24/10	This report was received from a nurse on 30OCT2009. A 21 year-old female initiated treatment with intravenous Soliris (eculizumab) for paroxysmal nocturnal hemoglobinuria (PNH). She received 600 mg Soliris infusions weekly from 13JAN2009 to 29JAN2009. <u>The patient missed her infusions for six weeks and 600 mg weekly infusions were restarted on 26MAR2009 until 21APR2009. She received her first 900 mg infusion on 28APR2009 and 900 mg infusions were scheduled for every two weeks. The patient was not compliant.</u> Since 28APR2009 she had received Soliris 900 mg on 18MAY2009, 02JUN2009, 16JUN2009 and 17JUL2009. She was restarted at 600 mg on 24SEP2009, missed a 600 mg infusion on 02OCT2009, received another 600 mg infusion on 09OCT2009, but did not return to receive additional infusions. The patient's platelet count started dropping in AUG2009. The patient's platelet counts were as follows: JUL2009 - 60000; AUG2009 - 43000; SEP2009 - 31000, and OCT2009 25000 to 26000. In (b) (6) the patient was "not feeling well" and took herself to the hospital. She received one unit of packed red blood cells. She was admitted the following day and received two units. The patient signed herself out of the hospital. Patient went to the Emergency Room (ER) on (b) (6), was transferred to another hospital and was subsequently admitted. She complained of weakness, body aches and heavy menstrual periods. Outcomes for the events were not provided. Medical history included PNH, aplastic anemia, chlamydial infection, left ovarian cyst, jaundice, ocular icterus, sonogram that was negative for pregnancy, periorbital hematoma, scleral hemorrhage and vomiting. Concomitant medication included tramadol (Ultram).The reporting nurse considered all of the events unrelated to Soliris.Follow-up information was received on 18NOV2009 from a physician and a hospital discharge summary.The patient was receiving 600 mg Soliris infusions weekly for four weeks, and then 900 mg infusions every other week. The patient missed a scheduled infusion on 22OCT2009.The patient, with recurrent anemia, stated that she had been feeling very fatigued and weak. On (b) (6), the patient felt too poorly to attend the clinic and was advised to go to the ER. A complete blood count (CBC) was performed in the ER, which revealed a platelet count of 20,000, hemoglobin of 6.4, hematocrit of 18.2, and a white blood cell count of 2.2. The patient also had cardiac enzymes, liver functions, and electrolytes that were normal, and a urine pregnancy test that was negative. She was transferred to another hospital after receiving one unit of packed red blood cells (PRBCs). The patient reported no change in weight, and was without fever, chills, cough, or chest pain. She had felt short of breath with exertion and generally weak, however these were attributed due to her anemia. There was no diarrhea or constipation, and the patient had daily bowel movements with no change in her urinary habits. The patient did report that her menstrual flow seemed to have increased, so that she now menstruates for approximately one week. A physical examination was within normal limits. Another two units of PRBCs were transfused before the patient left against medical advice (AMA) at approximately (b) (6) on (b) (6) prior to physician evaluation. The outcomes of the events were unknown. Diagnoses at discharge were anemia primary and aplastic anemia.Medical history included tubo-ovarian abscess and an unspecified abscess, bone marrow biopsy, miscarriage with subsequent dilation and curettage, smoking, social alcohol use, no allergies, and no other surgeries. The patient had a family history of cervical cancer in both her mother and sister, and diabetes.The physician did not report the causal relationship between the anemia and Soliris therapy.Follow-up information was received on 02DEC2009 from a physician and hospital records with additional information received on 02DEC2009 from a nurse.The physician and hospital records noted the patient received one unit of PRBCs in the ER and was transferred as a direct admission to another hospital. She had no active signs of bleeding or petechiae. Her last	Dose Omission

ISR NUM	RECV DATE	Narratives	Medication Error Type
		platelet count in (b) (6) was 26000 and at time of transfer, her platelet count was 20000. Additional prior laboratory results included hematocrit of 29 on 30SEP2009, hematocrit of 25 on 09OCT2009 and white blood cell count of 2.8 on 09OCT2009. Vital signs prior to transfer included temperature of 98.9, pulse of 82, blood pressure of 108/60 and oxygen saturation of 100% on room air. She was admitted on (b) (6) at (b) (6) for transfusion of three units of PRBCs for anemia. There was a delay in her transfusion, causing her to become upset and to want to leave. The patient was encouraged to stay and at (b) (6) her transfusion of PRBCs was started. Her second unit of PRBCs was completed on (b) (6) at (b) (6), and the patient refused the third unit of blood. The physician visited the patient and following conversation, the patient refused to stay and signed out AMA. Additional medical history included two previous transfusions of PRBCs in 2009 and one transfusion of blood or blood components in 2009. Additional concomitant medication included oxycodone (Roxicodone). The physician did not report the causal relationship of the anemia to Soliris therapy. The nurse reported that laboratory results on 01DEC2009 included hemoglobin of 6.3 and hematocrit of 18. The event of anemia remained ongoing. The nurse confirmed that the body aches were a symptom of heavy periods. She confirmed that the patient had not received a Soliris infusion since 09OCT2009, due to insurance issues. The nurse reported that the worsening anemia was not caused by Soliris therapy but instead was due to non-compliance. Company Comment 02DEC2009: Upon receipt of last follow-up, the pain was considered as a symptom of heavy periods. The case still remains a spontaneous, serious, medically confirmed report of anemia (with symptoms of weakness, fatigue, and shortness of breath with exertion), and platelet count decreased (medically significant). Anemia is listed in the CCDS, while platelet count decreased is unlisted. The other events are non-serious events. In agreement with the HCP's assessment, the company considers the events unrelated to Soliris, citing the fact that underlying PNH disease and co-morbidities are the most plausible explanations.	
7470632	5/10/11	This report was received from a healthcare professional (registered nurse) on 26APR2010. A patient initiated treatment with intravenous Soliris (eculizumab). Indication, dosages and administration schedule were not provided. <u>On an unspecified date, the patient received a 900 mg Soliris infusion diluted incorrectly in 210 mL of solution. Despite the total volume being 30 L more than per instructions, the patient was administered the entire solution.</u> No further information was provided. Medical history and concomitant medications were not provided. The nurse did not report the causal relationship between the event and Soliris therapy. Follow-up information was received on 07MAY2010 from a nurse: A 44 year-old female patient initiated treatment with intravenous Soliris for paroxysmal nocturnal hemoglobinuria. She received Soliris 600 mg weekly for the first four weeks from 10MAR2010 to 31MAR2010, and <u>then skipped a week before switching to 900 mg on 12APR2010.</u> The most recent infusion was noted to be on 28APR2010. The nurse reported that the patient did not experience any adverse events due to the drug administration error that occurred on 12APR2010. Medical history was not reported. Concomitant medications included multivitamins and calcium.	Dose Omission Wrong Dilution
6178111	5/4/09	This report was received from a consumer on 05FEB2009. A 44 year-old female initiated treatment with intravenous eculizumab (Soliris) for paroxysmal nocturnal hemoglobinuria (PNH). She received 900 mg Soliris infusion (date and frequency not provided). <u>On an unspecified date, instead of being infused with 180 cc of normal saline, the patient was infused with 1000 cc of normal saline. Reportedly, she received 900 mg of Soliris.</u> No ill effects were noted. Treatment with Soliris was ongoing. Medical history included PNH. Concomitant medications were not provided.	Wrong dilution
6177895	5/4/09	This report was received from a pharmacist on 31DEC2008. A patient initiated treatment with eculizumab (Soliris). Indication and administration dates were not provided. On an unspecified date, a pharmacist mixed 900 mg of Soliris in a pre-filled bag of dextrose 5% (D5) of 250 ml. The pharmacist withdrew some of the D5; however the total volume after adding Soliris was 280 ml. The infusion was approved for administration. Medical history and concomitant medications were not provided. Follow-up information was received on 07JAN2009 from the pharmacist and on 16JAN2009 from the patient. The pharmacist reported that the patient was a 60 year-old male. The event occurred on 31DEC2008. There were no reported adverse events after the infusion was administered. The patient reported that he initiated Soliris for paroxysmal nocturnal hemoglobinuria (PNH). He received the initial 600 mg and 900 mg infusions during a clinical trial. He continued to receive commercial 900 mg infusions every two weeks. Latest infusion was administered on 15JAN2009. The patient confirmed that he did not experience any adverse event after receiving his Soliris infusion on 31DEC2008. Medical history included PNH, rheumatic fever, irregular heartbeat, excess iron, and transfusion dependence. Concomitant medication included deferasirox (Exjade).	Wrong dilution

ISR NUM	RECV DATE	Narratives	Medication Error Type
6403942	10/16/09	This report was received from a nurse on 07JUL2009. A patient initiated treatment with intravenous Soliris (eculizumab). The patient received the first dose, <u>a 600 mg infusion, on an unspecified date. The first dose of Soliris was mixed with 120 ml of sodium chloride (saline), for a total volume of 180 ml, instead of diluting equal amounts of diluent and Soliris for a total volume of 120 ml.</u> Medical history and concomitant medications were not provided. Follow-up information was received on 13JUL2009 from the nurse. This 45 year-old female initiated treatment with Soliris for paroxysmal nocturnal hemoglobinuria (PNH). She received the initial 600 mg infusion on 30JUN2009 with an additional infusion on 07JUL2009. There was no complication due to the dilution error. On 04JUL2009, the patient received a blood transfusion and developed a severe headache that lasted two to three days. Treatment included acetaminophen (Tylenol). The nurse specified that the patient usually experienced headaches after blood transfusions. A third Soliris infusion was scheduled for 14JUL2009. Medical history included PNH, headaches, and blood transfusions. The patient was not taking any concomitant medication. The nurse was not sure if the headache was severe due to a combination of Soliris and blood transfusion.	Wrong dilution
7465821	5/9/11	This report was received from a consumer (patient) on 21APR2010. A 49-year-old female initiated treatment with intravenous Soliris (eculizumab). Indication, dosages and administration schedule were not provided. The most recent Soliris infusion was noted to be 900 mg on 20APR2010. On 20APR2010, <u>the patient reported that she received 900 mg Soliris infusion diluted in 100 cc of normal saline (NS). This was the first time the patient had received Soliris in 100 cc; usually it was mixed in a 250 cc bag. When contacted, a nurse from the physician's office confirmed that the pharmacy orders were to mix 900 mg of Soliris in 180 mL.</u> When contacted, the supervising nurse, who had administered the 900 mg of Soliris in 100 cc NS to the patient, was instructed on how to mix the dose properly in 180 mL of NS. An agreement was made to inservice the site staff again. Soliris therapy was ongoing. No further information was provided. Medical history and concomitant medications were not provided.	Wrong dilution
7467863	5/9/11	This report was received from a physician's assistant on 14JAN2011: A 44 year-old male received treatment with intravenous eculizumab (Soliris) for paroxysmal nocturnal hemoglobinuria (PNH). Soliris infusion dates and dosages were not provided. On 13JAN2011, <u>the patient received 600 mg of Soliris for his infusion (5th induction dose) instead of 900 mg because the office only received two vials instead of three vials of Soliris.</u> The patient will receive a 900 mg infusion on 20JAN2011 and then 900 mg bi-weekly, thereafter. No additional information was available. Medical history included PNH. Concomitant medications were not reported.	Wrong Dose
6200638	5/22/09	A 46 year-old female initiated treatment with intravenous (IV) Soliris for paroxysmal nocturnal hemoglobinuria (PNH). The initial 600 mg of Soliris was received on 28SEP2007 with additional 600 mg infusions received on 05OCT2007, 12OCT2007, and 19OCT2007. On 12OCT2007 and 19OCT2007, after the third and fourth infusions, the patient experienced nausea, vomiting, migraine-like headaches, and back pain. The back pain was described as 'kidney pain'. Treatment included an unspecified medication for the nausea and Aspirin for the migraine-like headache. Outcome of the events was unknown at the time of report. The patient's medical history included PNH and migraines. Concomitant medications were not provided. Follow-up was received on 28FEB2008. The patient received an additional Soliris 600 mg infusion on 26OCT2007. She received the first 900 mg infusion on 09NOV2007 with additional infusions on 26NOV2007, 12DEC2007, 21DEC2007, 03JAN2008, 23JAN2008, 04FEB2008, and 15FEB2008. Since SEP2007, the patient had experienced tightness in the neck and a headache during every infusion. On 12FEB2008, she also experienced weakness and shortness of breath, her white blood cell (WBC) count was elevated, and her hemoglobin level was 10. Per the patient, a physician diagnosed flu. On an unspecified date in FEB2008, the patient also experienced an episode of memory loss, described as being unable to remember her phone number and her license plate number. She was seen by a neurologist; a computerized tomography (CT) scan and a magnetic resonance imaging (MRI) were scheduled. The tightness in the neck and the headache were resolved on 15FEB2008. The memory loss was resolved in FEB2008. Outcome of flu, weakness, shortness of breath, and increased WBC count was not provided. <u>Follow-up was received on 06MAR2008 from the patient and from her physician. The Soliris infusion received on 26OCT2007 was not a 600 mg dose; it was the first 900 mg infusion.</u> The 03JAN2008 and 23JAN2008 infusions were cancelled. The patient received an additional 900 mg infusion on 05MAR2008. The patient reported that on 23JAN2008, she underwent a liver ultrasound; results were not provided. The memory loss happened on 31JAN2008, not FEB2008 and it resolved on the same day. On 15FEB2008, the patient experienced a stiff neck, which developed into a headache worse than any migraine and so painful that she "could not touch her hair". The stiff neck resolved 15FEB2008. The headache resolved 17FEB2008 after treatment with acetylsalicylic acid (aspirin). The flu resolved in FEB2008 without treatment. The shortness of breath and the weakness resolved in FEB2008. An MRI was scheduled for 07MAR2008. The patient was to see her physician on 12MAR2008.	Wrong dose

ISR NUM	RECV DATE	Narratives	Medication Error Type
		Next Soliris infusion was scheduled for 17MAR2008. The physician specified that the Soliris infusions of 03JAN2008 and 23JAN2008 were missed due to insurance issues. After the missed Soliris doses, the patient did not receive reinduction doses but continued with the 900 mg dosage. The physician did not feel that the shortness of breath, weakness, or increased WBC count were related to Soliris. She considered that the shortness of breath and the weakness were due partly to the flu and partly to the anemia. Furthermore, the physician considered the headaches related to Soliris. Follow-up was received on 07MAY2008 from a physician. The abdominal ultrasound with complete abdominal Doppler performed on 23JAN2008 showed that the liver was homogeneous, the portal vein and hepatic veins were patent, and there were a few gallbladder polyps. White blood cell count (WBC) was increased to 15.41 on 08FEB2008. On 15FEB2008 WBC was 5.92 and remained within normal limits at 6.17 on 05MAR2008, 5.14 on 17MAR2008, 7.81 on 03MAR2008, and 5.79 on 31MAR2008. The flu, nausea, memory loss, shortness of breath, backache, weakness, vomiting, and increased white blood cell count all were resolved on unspecified dates. The physician assessed the headaches as probably due to Soliris. The other events were related to PNH or the flu (increased WBC). Follow-up was received on 24JUN2008 from the patient. The patient received additional 900 mg Soliris infusions on 17MAR2008, 28MAR2008, 08APR2008, 18APR2008, 29APR2008, 12MAY2008, 23MAY2008, 03JUN2008, and 13JUN2008. In 2008, the patient was still jaundiced, her liver functions were still elevated, her hemoglobin was not stabilized, and she was fatigued. In 2008, her hemoglobin level was 7.5. She received bimonthly transfusions packed cells. Starting in 2008 on the eight or ninth day of her 12-day Soliris infusion schedule, she had dark colored urine associated with kidney pain. On 20JUN2008, she was transfused with packed cells and her hemoglobin level increased to 12. The events were ongoing. Additional medical history included elevated liver enzymes (prior to Soliris therapy), and abdominal pain. Concomitant medications included hydroxyzine (Atarax), folic acid, escitalopram oxalate (Lexapro), amitriptyline, and ferric gluconate.	
6177734	5/4/09	This report was received from a physician's office employee on 22DEC2008. A female patient initiated treatment with eculizumab (Soliris). Indication, dosages, and administration dates prior to the event were not provided. <u>On 18DEC2008, the patient received a Soliris 600 mg dose instead of the scheduled 900 mg dose, as one of the vials was broken and the office was not able to obtain a replacement locally. Medical history and concomitant medications were not provided. Follow-up information was received on 05JAN2009 from a nurse. The female patient initiated treatment with Soliris for paroxysmal nocturnal hemoglobinuria (PNH). The nurse confirmed that the patient received a 600 mg Soliris infusion instead of a 900 mg infusion on 18DEC2008. The 900 mg vial of Soliris was broken and no other 900 mg vials were available. The patient did not experience side effects from the lower dose.</u> The patient had been receiving 900 mg Soliris infusions for quite a while per the nurse. Medical history included PNH. Follow-up information was received on 28JAN2009 from a nurse. The 24 year-old patient received her first 600 mg infusion on 24SEP2008, and switched to 900 mg infusions every two weeks since 22OCT2008. Her most recent 900 mg infusions were on 26DEC2008, 09JAN2009, and 23JAN2009. The patient received a 900 mg Soliris infusion on 26DEC2008, approximately one week after receiving the lower dose infusion. Medical history included hypercoagulation. Concomitant medications included folate, hydrocodone/paracetamol (Vicodin), and warfarin.	Wrong dose
6177915	5/4/09	This report was received from a nurse on 02JAN2009 and on 08JAN2009. A 31 year-old female initiated treatment with intravenous eculizumab (Soliris) for paroxysmal nocturnal hemoglobinuria (PNH). She received the initial infusion in 2006 during a clinical trial and the first commercial 900 mg infusion on 17MAY2007. On 02JAN2009, a technician broke a Soliris vial. As a result, the patient received only 600 mg of Soliris on 02JAN2009 and the remaining 300 mg on 06JAN2009. Medical history included PNH, nausea, restless leg syndrome, anxiety, migraines, difficulty sleeping, narcotic abuse, and abdominal pain. Concomitant medications included warfarin sodium (Coumadin), promethazine (Phenergan), folic acid, ropinirole hydrochloride (Requip), and fentanyl. The nurse considered the event not related to Soliris therapy.	Wrong dose
6404143	10/16/09	This report was received from a registered nurse on 28SEP2009 and 30SEP2009. A 62-year-old male initiated treatment with intravenous Soliris (eculizumab) for paroxysmal nocturnal hemoglobinuria (PNH). He received 600 mg infusions weekly for the first four weeks from 24AUG2009. <u>On 21SEP2009, the patient received 600 mg of Soliris instead of 900 mg for the week 5 dose.</u> The patient was rescheduled to receive the first 900 mg Soliris infusion on 05OCT2009. On 21SEP2009, the event was considered to be resolved. No adverse events occurred in response to the dose administration error. Medical history included PNH, myelodysplastic syndrome (MDS), monthly transfusions, rotator cuff surgery, blood clot in the femoral artery, and past use of acetylsalicylic acid (Aspirin) 81 mg which caused bruising. Concomitant medications included omeprazole (Prilosec), erythropoietin (Procrit), folic acid, filgrastim (Neupogen), and dexamethasone (Decadron).	Wrong Dose

ISR NUM	RECV DATE	Narratives	Medication Error Type
6404068	10/16/09	This report was received from a physician and pharmacist on 08SEP2009. A 56 year-old female received a <u>200 mg infusion of intravenous Soliris (eculizumab) in error on 08SEP2009.</u> The patient, who had a colon cancer, was treated with oxaliplatin (Eloxatine), methylprednisolone sodium succinate (Solu-Medrol), and ondansetron hydrochloride (Zophren). <u>Bag names were inverted after preparation and the patient received by mistake 200 mg of Soliris instead of oxaliplatin on 08SEP2009 at 14:30.</u> No adverse event occurred, neither during the Soliris infusion or immediately after. Before the Soliris infusion, the patient had received methylprednisolone sodium succinate, 'mediafoline', and ondansetron hydrochloride. She did not receive oxaliplatin. It was noted that the patient had not received a meningococcal vaccination. Minimization measures were taken immediately regarding the risk of meningococcal infection. The patient received prophylactic antibiotherapy. Outcome was unknown. Medical history included colon cancer. Concomitant medications included oxaliplatin, methylprednisolone sodium succinate, ondansetron hydrochloride, and mediafoline. The reporting physician considered the drug administration error unrelated to Soliris therapy.	Wrong drug
6548005	1/24/10	This report was received from a consumer on 09DEC2009. A 36 year old female received treatment with intravenous Soliris (eculizumab). Indication, dates and doses of treatment were not provided. During the last Soliris infusion, the patient complained of tingling down her spine. The infusion was slowed down and the symptoms abated. No additional information was provided. Medical history and concomitant medications were not provided. Follow-up information was received on 17DEC2009 from a nurse. The patient received treatment with intravenous Soliris (eculizumab) for paroxysmal nocturnal hemoglobinuria (PNH). She received 600 mg Soliris infusions weekly for the first four weeks from 12NOV2009 until 06DEC2009, and switched to 900 mg infusions on 16DEC2009. On 24NOV2009, the patient felt a little bit of tingling down the spine during her Soliris infusion. The patient recovered from the event on 24NOV2009. The nurse reported that the next infusion was slowed and the patient had no repeat of event. No treatment was rendered. <u>The nurse also reported that the physician realized the first 900 mg infusion should have been one week after the 4th 600 mg infusion, however, since the dose had already been ordered for 16DEC2009, the patient received her 900 mg infusion at that time.</u> Medical history included PNH. Concomitant medications included baclofen, folic acid, propranolol and acetylsalicylic acid (Aspirin). The nurse reported that the tingling down spine was not related to Soliris therapy and that the first 900 mg infusion should have been one week after the 4th 600 mg infusion was not related to Soliris therapy but due to an error in ordering of the dose.	Wrong frequency of administration

Appendix C: Case listings from AERS Database

ISR NUM	ISR NUM
6200838	6177734
6200853	6177915
6200054	6200408
6404054	6200765
6677887	6404143
7467878	7435106
6200789	6200646
6200905	6200773
6200833	6178617
6200804	6403942
7137845	6404068
7465995	6548005
7467863	6677381
6199759	7467875
6178111	6677860
6200638	6944749
6200760	7381256
6894638	7465821
6177895	6200827
6547874	6200785
7044854	6200434
7468054	6548026
6200738	7280883
7470632	

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: August 26, 2011

TO: Ebla Ali Ibrahim, M.S., Regulatory Project Manager
Martha Donoghue, M.D., Medical Officer
Division of Hematology Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

THROUGH: Jean Mulinde, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

SUBJECT: Evaluation of Clinical Inspections.

BLA: 125166 STN-172

APPLICANT: Alexion Pharmaceuticals, Inc.

DRUG: Eculizumab (Soliris®)

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: For the treatment of atypical Hemolytic Uremic Syndrome (aHUS)

CONSULTATION REQUEST DATE: 4/27/2011

DIVISION ACTION GOAL DATE: 9/24/2011

PDUFA DATE: 9/24/2011

I. BACKGROUND:

Alexion Pharmaceuticals Inc. seeks licensure to market eculizumab for the treatment of atypical hemolytic uremic syndrome (aHUS), an extremely rare, progressive, and life-threatening disease characterized as a thrombotic microangiopathic hemolytic anemia (TMA) and impaired renal function. aHUS is caused by chronic uncontrolled complement activation, which puts patients at constant risk for either subacute or acute, progressive complications of TMA in multiple organs, including the brain, heart, and/or kidneys. Because of uncontrolled complement activation, the risk of severe, sudden acceleration of disease with life-threatening complications is lifelong, and the timing of occurrence of these complications is unpredictable.

Within the first year of diagnosis, the majority of patients either die or progress to end-stage renal disease requiring long-term dialysis. There are currently very limited treatment options for patients with aHUS. Therapy is reportedly empirical and aimed primarily at stabilizing the patient and mitigating irreversible kidney damage primarily through the use of Plasma Therapy (PT), and can include the use of immunosuppressant drugs and supportive care. aHUS is a very rare disease with sparse epidemiologic data in the literature, with most patients developing the disease before 10 years of age at an estimated 3 per million children (< 18 years of age), and even lower prevalence in adults.

Eculizumab is a humanized monoclonal antibody which binds uniquely to human complement protein C5 and inhibits terminal complement activation. The current BLA is supported primarily by data from 3 pivotal studies. Two prospective controlled, open-label single-arm studies; C08-002A/B (entitled, "An Open-Label, Multi-Center Controlled Clinical Trial of Eculizumab in Adult/Adolescent Patients with Plasma Therapy-Resistant Atypical Hemolytic-Uremic Syndrome (aHUS)") and C08-003A/B (entitled, "An Open-Label, Multi-Center Controlled Clinical Trial of Eculizumab in Adult/Adolescent Patients with Plasma Therapy-Sensitive Atypical Hemolytic-Uremic Syndrome (aHUS)"), were conducted in adult and adolescent patients with aHUS. In addition, a retrospective data collection study, Study C09-001r (entitled, "A Retrospective, Observational, Non-Interventional Trial to Assess Eculizumab Treatment Effect in Patients with Atypical Hemolytic Uremic Syndrome (aHUS)"), captured information on adult and pediatric patients who received eculizumab outside of the prospective clinical studies above. The application includes data from a total of 67 patients, 37 from the prospective studies and 30 from the retrospective studies. There are 15 pediatric patients (all from the retrospective study), 10 adolescents (6 from the prospective studies and 4 from the retrospective study), and 42 adults (31 from the prospective studies and 11 from the retrospective study).

Regarding the prospective studies, the planned enrollment for study C08-002A/B was 15 subjects; C08-002A for adults ≥ 18 years of age, and C08-002B for adolescents between 12 and 18 years of age weighing >40 kg. The study enrolled and treated 17 subjects at a total of 15 clinical sites; U.S. (6), France (5), Germany (2), and the U.K. and Austria (1 site each). The planned enrollment for study C08-003A/B was 30 subjects, C08-003A for adults ≥ 18 years of age, and C08-003B for adolescents between 12 and 18 years of age weighing >40 kg. The study enrolled 23 subjects, with 20 subjects actually treated, at a total of 12 clinical sites; France (5), U.K. (2), and Canada, Germany, Italy, Sweden and the Netherlands (1 site each).

Regarding the retrospective study, the planned enrollment for study C09-001r was defined as, “all patients who had been diagnosed with aHUS and had received at least one dose of eculizumab treatment for aHUS (since the approval of eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) by the FDA and EMA) between 2007 and December 2009 outside of an Alexion-sponsored controlled clinical trial.” Thirty six patients who were diagnosed with aHUS and had been treated with eculizumab were identified. Data from 30 of 36 patients were used for this retrospective trial. A total of 6 subjects were not included in the study for the following reasons; 2 subjects declined participation, and the treating clinicians for the other 4 subjects declined participation in the retrospective trial.

Eight clinical sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811). The studies sponsor, Alexion Pharmaceuticals, Inc., was also inspected, in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810).

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI#1: Site #198 Christopher Legendre Hôpital Necker-Enfants Malades, Service de Transplantation Rénale adulte et Soins Intensifs 149, rue de Sèvres, 75743 Paris Cedex 15 France	Protocol: C08-002A/B, C08-003A/B Site Number: 198 Number of Subjects: 2, 3	July 18-22, 2011	Pending Interim classification: NAI
CI#2: Site #197 Yahsou Delmas CHU Pellegrin, Département de Néphrologie, Unité d'hémodialyse, Place Amélie Raba Léon, 33076 Bordeaux cedex France	Protocol: C08-002A/B, C08-003A/B Site Number: 197 Number of Subjects: 1, 2	August 4-5, 2011	Pending Interim classification: NAI
CI#3: Site #196 Maryvonne Hourmant Hôtel Dieu-CHU de Nantes, Service de, Néphrologie et d'Immunologie Clinique, 30 boulevard Jean Monnet. 44093 Nantes Cedex 1 France	Protocol: C08-002A/B, C08-003A/B Site Number: 196 Number of Subjects: 1, 2	August 1-2, 2011	Pending Interim classification: NAI
CI#4: Site #191 Veronique Baudouin Hôpital Robert Debrém, Service Nephrologie, 48, Boulevard Sérurier, 75935 Paris Cedex 19	Protocol: C09-001r Site Number: 191 Number of Subjects: 1	July 25-26, 2011	Pending Interim classification: NAI
CI#5: Site #192 Mary Alice Macher AP-DP Hôpital Robert Debré, Service Nephrologie, 48, Boulevard Sérurier, 75935 Paris Cedex 19	Protocol: C09-001r Site Number: 192 Number of Subjects: 1	July 28, 2011	Pending Interim classification: NAI

Name of CI or Sponsor/CRO, Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI#6: Site #015 Jodi Smith Seattle Children's, 4800 Sand Point Way NE, P.O. Box 50020, Seattle, WA 98105	Protocol: C09-001r Site Number: 015 Number of Subjects: 1	June 2-10, 2011	Pending Interim classification: NAI
CI#7: Site #013 Julius Sherwinter Children's Healthcare of Atlanta, Children's Kidney Center, 5501 Chamblee Dunwoody Rd, Atlanta, GA 30338	Protocol: C09-001r Site Number: 013 Number of Subjects: 1	July 5-8, 2011	Pending Interim classification: NAI
CI#8: Site #022 Ralph Gruppo Cincinnati Children's Hospital, Division of Hematology & Oncology, 3333 Burnet Avenue Suigte 100-L1, Cincinnati, OH 45229	Protocol: C09-001r Site Number: 022 Number of Subjects: 1	June 14-17, 2011	Pending Interim classification: NAI
Sponsor: Alexion Pharmaceuticals, Inc. 352 Knotter Drive Cheshire, CT 06410	Protocol: C08-002A/B Site Numbers: 198, 197, 196 Protocol: C08-003A/B Site Numbers: 198, 197, 196 Protocol: C09-001r Site Numbers: 191, 192, 015, 013, 022	August 3-16, 2011	Pending Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field and EIR has not been received from the field or complete review of EIR is pending and final classification letter has not issued.

1. CI#1: – Dr. Christopher Legendre
(Site Number 198)

- a. What was inspected:** Regarding study C08-002A/B, the site screened and enrolled 2 subjects. Regarding study C08-003A/B, the site screened and enrolled 3 subjects. The study records of all subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, and test article accountability.

Note: The EIR was not available at the time this CIS was written. The general observations described below are based on preliminary communications from the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocols was found to be good. There was no evidence of underreporting AEs. The primary efficacy endpoint data were verified. The diagnosis of aHUS was confirmed using key inclusion criteria; platelet, LDH, creatinine and plasma therapy parameters. Study assessment of platelet counts, LDH, serum creatinine and presence/absence of plasma infusion, plasma exchange, dialysis and/or renal transplantation was reviewed. Measurement of platelet counts, LDH and serum creatinine levels appeared to be collected according to the protocol. Samples were processed by the site and sent to the sponsor's [Alexion] central laboratory for testing. Laboratory results for platelets, serum creatinine, and LDH received from a central laboratory were verified. PK/PD samples were processed by the site and sent to the sponsor for assay. PK/PD collection date/time was verified. PK/PD results were not received by the site; therefore, data was not verified. The site did not maintain documentation of PK/PD sample processing.

Consistent with the routine clinical investigator compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125166 STN-172 were compared and verified. No deficiencies were noted. A Form FDA 483 was not issued.

- c. Assessment of data integrity:** The data for Dr. Legendre's site, associated with Studies C08-002A/B and C08-003A/B submitted to the Agency in support of BLA 125166 STN-172, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the final EIR.

2. CI#2: Dr. Yahsou Delmas
(Site Number 197)

- a. What was inspected:** Regarding study C08-002A/B, the site screened and enrolled 1 subject. Regarding study C08-003A/B, the site screened and enrolled 2 subjects. The study records of all subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, and test article accountability.

Note: The EIR was not available at the time this CIS was written. The general observations described below are based on preliminary communications from the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocols was found to be good. There was no evidence of underreporting AEs. The primary efficacy endpoint data were verified. The diagnosis of aHUS was confirmed using key inclusion criteria; platelet, LDH, creatinine and plasma therapy parameters. Study assessment of platelet counts, LDH, serum creatinine and presence/absence of plasma infusion, plasma exchange, dialysis and/or renal transplantation was reviewed. Measurement of platelet counts, LDH and serum creatinine levels appeared to be collected according to the protocol. Samples were processed by the site and sent to the sponsor's [Alexion] central laboratory for testing. Laboratory results for platelets, serum creatinine, and LDH received from a central laboratory were verified. PK/PD samples were processed by the site and sent to the sponsor for assay. PK/PD collection date/time was verified. PK/PD results were not received by the site; therefore, data was not verified. The site did not maintain documentation of PK/PD sample processing.

Consistent with the routine clinical investigator compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125166 STN-172 were compared and verified. No deficiencies were noted. A Form FDA 483 was not issued.

- c. Assessment of data integrity:** The data for Dr. Delmas' site, associated with Studies C08-002A/B and C08-003A/B submitted to the Agency in support of BLA 125166 STN-172, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the final EIR.

3. CI#3: Dr. Maryvonne Hourmant
(Site Number 196)

- a. What was inspected:** Regarding study C08-002A/B, the site screened and enrolled 1 subject. Regarding study C08-003A/B, the site screened and enrolled 2 subjects. The study records of all subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, and test article accountability.

Note: The EIR was not available at the time this CIS was written. The general observations described below are based on preliminary communications from the FDA

field investigator. An inspection summary addendum will be generated if conclusions change upon review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocols was found to be good. There was no evidence of underreporting AEs. The primary efficacy endpoint data were verified. The diagnosis of aHUS was confirmed using key inclusion criteria; platelet, LDH, creatinine and plasma therapy parameters. Study assessment of platelet counts, LDH, serum creatinine and presence/absence of plasma infusion, plasma exchange, dialysis and/or renal transplantation was reviewed. Measurement of platelet counts, LDH and serum creatinine levels appeared to be collected according to the protocol. Samples were processed by the site and sent to the sponsor's [Alexion] central laboratory for testing. Laboratory results for platelets, serum creatinine, and LDH received from a central laboratory were verified. PK/PD samples were processed by the site and sent to the sponsor for assay. PK/PD collection date/time was verified. PK/PD results were not received by the site; therefore, data was not verified. The site did not maintain documentation of PK/PD sample processing.

Consistent with the routine clinical investigator compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125166 STN-172 were compared and verified. No deficiencies were noted. A Form FDA 483 was not issued.

- c. Assessment of data integrity:** The data for Dr. Hourmant's site, associated with Studies C08-002A/B and C08-003A/B submitted to the Agency in support of BLA 125166 STN-172, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the final EIR.

4. CI#4: – Dr. Veronique Baudouin
(Site Number 191)

- a. What Was Inspected:** The C09-001r [retrospective] study records of the one treated subject were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, test article accountability, and PK/PD sampling.

The following application specific data listings were verified:

Listing 16.2.4.1a: Demographic Characteristics

Listing 16.2.4.8: aHUS Exacerbation Signs and Symptoms

Listing 16.2.4.3a: aHUS exacerbations and Associated Triggering Conditions Initiating Treatment

Listing 16.2.4.3b: aHUS Exacerbations and Associated Triggering Conditions During Treatment

Listing 16.2.4.1b: Demographic Characteristics - Genetic Data
Listing 16.2.4.5: aHUS Exacerbation Dialysis History
Listing 16.2.4.2: Medical History
Listing 16.2.4.6: aHus Exacerbation Plasma Therapy History
Listing 16.2.7.1.1a and 16.2.7.1.1b Adverse Events
Listing 16.2.7.1.2 Adverse Events
Listing 16.2.7.1.6 Reason for Discontinuation of Eculizumab
Listing 16.2.6.2: Plasma Therapy during study
Listing 16.2.6.1: Dialysis During Study
Listing 16.2.6.3: Blood Transfusion Record After First Dose
Listing 16.2.5.3: Investigational Drug Administration Date and Time
Listing 16.2.8.2a: Hematology (Platelet),
Listing 16.2.8.1: Chemistry / 16.2.8.4a Hemolytic Markers (LDH)
Listing 16.2.8.1: Chemistry (Creatinine)
Listing 16.2.8.2a Hematology (Hemoglobin)
Listing 16.2.9.1 Vital Signs

Note: The EIR was not available at the time this CIS was written. The general observations described below are based on preliminary communications from the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be good. The site screened/enrolled one subject. The data listings were verified and there was no evidence of underreporting AEs.

Consistent with the routine clinical investigator compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125166 STN-172 were compared and verified. No deficiencies were noted. A Form FDA 483 was not issued.

- c. Assessment of data integrity:** The data for Dr. Baudouin's site, associated with Study C09-001r submitted to the Agency in support of BLA 125166 STN-172, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the final EIR.

5. CI#5: -- Dr. Mary Alice Macher
(Site Number 192)

- a. What Was Inspected:** The C09-001r [retrospective] study records of the one treated subject were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, and reporting of AEs in

accordance with the protocol. The FDA field investigator also assessed informed consent documents, test article accountability, and PK/PD sampling.

The following application specific data listings were verified:

Listing 16.2.4.1a: Demographic Characteristics
Listing 16.2.4.8: aHUS Exacerbation Signs and Symptoms
Listing 16.2.4.3a: aHUS exacerbations and Associated Triggering Conditions Initiating Treatment
Listing 16.2.4.3b: aHUS Exacerbations and Associated Triggering Conditions During Treatment
Listing 16.2.4.1b: Demographic Characteristics - Genetic Data
Listing 16.2.4.5: aHUS Exacerbation Dialysis History
Listing 16.2.4.2: Medical History
Listing 16.2.4.6: aHus Exacerbation Plasma Therapy History
Listing 16.2.7.1.1a and 16.2.7.1.1b Adverse Events
Listing 16.2.7.1.2 Adverse Events
Listing 16.2.7.1.6 Reason for Discontinuation of Eculizumab
Listing 16.2.6.2: Plasma Therapy during study
Listing 16.2.6.1: Dialysis During Study
Listing 16.2.6.3: Blood Transfusion Record After First Dose
Listing 16.2.5.3: Investigational Drug Administration Date and Time
Listing 16.2.8.2a: Hematology (Platelet),
Listing 16.2.8.1: Chemistry / 16.2.8.4a Hemolytic Markers (LDH)
Listing 16.2.8.1: Chemistry (Creatinine)
Listing 16.2.8.2a Hematology (Hemoglobin)
Listing 16.2.9.1 Vital Signs

Note: The EIR was not available at the time this CIS was written. The general observations described below are based on preliminary communications from the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be good. The site screened/enrolled one subject. The data listings were verified and there was no evidence of underreporting AEs. The subject died on [REDACTED] (b) (6) of cardiac arrest. The subject suffered from a massive stroke after surgery for right carotid artery stenosis. The site collected PK/PD samples; however, samples were not received/assayed in time to be included in data listings.

Consistent with the routine clinical investigator compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125166 STN-172 were compared and verified. No deficiencies were noted. A Form FDA 483 was not issued.

- c. Assessment of data integrity:** The data for Dr. Macher's site, associated with Study C09-001r submitted to the Agency in support of BLA 125166 STN-172, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the final EIR.

6. CI#6: – Dr. Jodi Smith
(Site Number 015)

- a. What Was Inspected:** The C09-001r [retrospective] study records of the one treated subject were audited in accordance with the clinical investigator compliance program, CP 7348.811. During this inspection, documents reviewed included the study protocol; IRB approval of the protocol, source documents (medical records) and the paper case report form for the single subject in the study. Record review included inclusion/exclusion criteria for the subjects; adverse events; serious adverse event reporting; and the informed consent for the subject. The director of the pharmacy was interviewed about dispensing the drug, eculizumab, for infusion. Because this study was a retrospective, record review, there were not drug accountability records available for review.

Note: The EIR was not available at the time this CIS was written. The general observations described below are based on preliminary communications from the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The site screened/enrolled one subject. The data listings were verified for key efficacy endpoint parameters. However, there were inconsistencies in identification and reporting/recording AEs. Per protocol, adverse reactions are defined as adverse drug reactions or as adverse reactions of interest. The definition of AEs in the protocol seems to have limited what was collected by the monitors. As a result, the clinical investigator informed that [they] were only looking for the "pre-specified AEs of special interest." The clinical investigator identified the AEs that met these criteria for the monitors. However, Dr. Smith recognized that what is typically meant as an AE, were not captured due to protocol restrictions. Because of the definition for AE in the protocol, and the overwhelming amount of medical records for this one subject, the FDA field investigator was only able to identify and verify a subset of AEs in the medical records.

The site did not collect blood samples for PK/PD. The subject had extensive paper medical records, 13 paper volumes, and uncountable electronic medical records. The subject received 20 doses of the drug during the study period. The sponsor monitors were only on site apparently for 3 days according to the site personnel. The FDA field investigator speculated that as a result of the limited amount of time allocated to the monitor to collect data from the source records, the monitor was unable to accurately capture data beyond the key efficacy and safety parameters; LDH, platelet counts, and creatinine.

Consistent with the routine clinical investigator compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125166s172 were compared and verified for key efficacy and safety parameters. Due to the extensive medical records for this subject the monitors did not have adequate time to record all but the most critical efficacy and safety data. A Form FDA 483 was issued, however, it should be noted that the deficiencies (see summarized below) are actually attributable to the sponsor-specific monitors and not the clinical investigator or the site as the CRO monitor was responsible for review of the subjects' source documents and completion of the CRF according to the investigational plan. For this site, only the key efficacy and safety parameters were recorded by the monitors in the CRF, and these items were verified during the inspection against data listings submitted to BLA 125166 STN-172.

The Form FDA 483 reported recordkeeping inspection observations. Briefly, not all data points were recorded accurately by the monitors, resulting in numerous lab values of "NA" when source documents demonstrated that there were laboratories performed, and there were some transcription errors noted between the source records and the CRF. Notable observations from the Form FDA 483 that are directly related to key efficacy and safety parameters are as follows:

- The subject received a first dose of study drug on 6/16/09, with plasmapheresis immediately prior to the dose. However, the CRF did not record this plasmapheresis event.
 - The subject was first diagnosed with aHUS on 1/12/05 and had subsequent testing for C3, C4, or Complement Total on 1/15/05 and 1/22/05, however, these laboratory results were not recorded in the CRF.
 - The CRF states that the subject received a drug dose on 10/13/09; however, no dose was given on that date. The subject received the next dose on 10/16/09, which was not recorded in the CRF.
 - Vitals including BP, weight and height on the day of dosing were not always recorded accurately on the CRF or were not recorded. Transcription errors appeared to be minor deviations.
- c. **Assessment of data integrity:** Notwithstanding the observations noted above, the data for Dr. Smith's site, associated with Study C09-001r submitted to the Agency in support of BLA 125166 STN-172, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the final EIR.

7. CI#7: – Dr. Julius Sherwinter
(Site Number 013)

- a. **What Was Inspected:** The C09-001r [retrospective] study records of the one treated subject were audited in accordance with the clinical investigator compliance program,

CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, test article accountability, and PK/PD sampling.

The following application specific data listings were verified:

Listing 16.2.4.1a: Demographic Characteristics
Listing 16.2.4.8: aHUS Exacerbation Signs and Symptoms
Listing 16.2.4.3a: aHUS exacerbations and Associated Triggering Conditions Initiating Treatment
Listing 16.2.4.3b: aHUS Exacerbations and Associated Triggering Conditions During Treatment
Listing 16.2.4.1b: Demographic Characteristics - Genetic Data
Listing 16.2.4.5: aHUS Exacerbation Dialysis History
Listing 16.2.4.2: Medical History
Listing 16.2.4.6: aHUS Exacerbation Plasma Therapy History
Listing 16.2.7.1.1a and 16.2.7.1.1b Adverse Events
Listing 16.2.7.1.2 Adverse Events
Listing 16.2.7.1.6 Reason for Discontinuation of Eculizumab
Listing 16.2.6.2: Plasma Therapy during study
Listing 16.2.6.1: Dialysis During Study
Listing 16.2.6.3: Blood Transfusion Record After First Dose
Listing 16.2.5.3: Investigational Drug Administration Date and Time
Listing 16.2.8.2a: Hematology (Platelet),
Listing 16.2.8.1: Chemistry / 16.2.8.4a Hemolytic Markers (LDH)
Listing 16.2.8.1: Chemistry (Creatinine)
Listing 16.2.8.2a Hematology (Hemoglobin)
Listing 16.2.9.1 Vital Signs

Note: The EIR was not available at the time this CIS was written. The general observations described below are based on preliminary communications from the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The site screened/enrolled one subject. The data listings were verified with only minor inspectional observations. The only discrepancies between the data listings and the records at the site basically relate to the outpatient infusion vitals and start and stop times. The key efficacy endpoint parameters were verified. There was no evidence of underreporting AEs.

Consistent with the routine clinical investigator compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125166 STN-172 were compared and verified. No significant deficiencies were noted. A Form FDA 483 was not issued.

- c. **Assessment of data integrity:** The data for Dr. Sherwinter's site, associated with Study C09-001r submitted to the Agency in support of BLA 125166 STN-172, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the final EIR.

8. CI#8: – Dr. Ralph Gruppo
(Site Number 022)

- a. **What Was Inspected:** The C09-001r [retrospective] study records of the one treated subject were audited in accordance with the clinical investigator compliance program, CP 7348.811. Documents reviewed include; IRB approval of the protocol and informed consent, case report forms, source documents, medical records, data end points, and adverse events.

The following application specific data listings were verified:

Listing 16.2.4.1a: Demographic Characteristics

Listing 16.2.4.8: aHUS Exacerbation Signs and Symptoms

Listing 16.2.4.3a: aHUS exacerbations and Associated Triggering Conditions Initiating Treatment

Listing 16.2.4.3b: aHUS Exacerbations and Associated Triggering Conditions During Treatment

Listing 16.2.4.1b: Demographic Characteristics - Genetic Data

Listing 16.2.4.5: aHUS Exacerbation Dialysis History

Listing 16.2.4.2: Medical History

Listing 16.2.4.6: aHus Exacerbation Plasma Therapy History

Listing 16.2.7.1.1a and 16.2.7.1.1b Adverse Events

Listing 16.2.7.1.2 Adverse Events

Listing 16.2.7.1.6 Reason for Discontinuation of Eculizumab

Listing 16.2.6.2: Plasma Therapy during study

Listing 16.2.6.1: Dialysis During Study

Listing 16.2.6.3: Blood Transfusion Record After First Dose

Listing 16.2.5.3: Investigational Drug Administration Date and Time

Listing 16.2.8.2a: Hematology (Platelet),

Listing 16.2.8.1: Chemistry / 16.2.8.4a Hemolytic Markers (LDH)

Listing 16.2.8.1: Chemistry (Creatinine)

Listing 16.2.8.2a Hematology (Hemoglobin)

Listing 16.2.9.1 Vital Signs

Note: The EIR was not available at the time this CIS was written. The general observations described below are based on preliminary communications from the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon review of the EIR.

- b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The site screened/enrolled one subject. The data listings were assessed and there was no evidence of underreporting AEs. However,

there were discrepancies observed between the source document and CRF and data line listings. Noteworthy observations relating directly to key study parameters/line listings (described above) are provided here. These observations appear to be driven by the fact that the subjects had numerous assessments done for these efficacy relevant assessments; platelets, LDH, creatinine and hemoglobin, and sometimes multiples on the same date. In all cases there were near adjacent assessments reported (within one day of the missing assessments) or there were more than one test result available for a given date and the “monitors” selected only one measurement to record in the CRF. There was no evidence to suggest a systematic bias in selection of data recorded in the CRF under these circumstances. The reliability of efficacy and safety data for this site’s one subject should be unaffected by the observations below.

- The subject received a dose of study drug on 11/16/09; however, the CRF did not record this dosing, nor is it captured in the data listings.
- Vitals including BP, weight and height on the day of dosing were not always recorded accurately on the CRF or were not recorded. Transcription errors appeared to be minor deviations.
- With respect to platelet assessments during the pretreatment period (-30 days, beginning on 7/27/08) and treatment period (8/27/08 to 12/20/09) the source documents list 5 platelet test results, but these were not specifically listed in the CRF or data listings for those dates. Review of the data listings show that similar platelet values were reported either on the same date or within one day of the “missing” values and in all cases the values reported on an adjacent date were very similar to the missing values found in the source records. The missing platelet values found in the source records but not in the CRF or data listings should have no impact on efficacy endpoint assessments for this subject.
- With respect to creatinine assessments during the pretreatment (-30 days, beginning on 7/27/08) and treatment period (8/27/08 to 12/20/09) there were 4 dates where the source documents listed creatinine values but these were not specifically listed in the CRF or data listings for those dates. Review of the data listings show that creatinine values were reported within one day of the “missing” values and in all 4 cases the values reported on the prior date were nearly identical to the missing values found in the source records. The minor discrepancies in creatinine values recorded in the CRF and data listings should have no impact on efficacy endpoint assessments for this subject.
- With respect to LDH assessments during the pretreatment (-30 days, beginning on 7/27/08) and treatment period (8/27/08 to 12/20/09) there were 2 dates where the source documents listed LDH values but these were not specifically listed in the data listings for those dates. Review of the data listings shows that LDH assessments were reported on one date prior to or after the dates of missing LDH assessments. It appears that the available LDH values adjacent to the date of missing LDH values are similar in value and results to those available in the data listings. It is unclear why the sponsor omitted records for these LDH values but the missing LDH values should have no impact on study endpoint assessments.
- With respect to hemoglobin assessments during the pretreatment (-30 days, beginning on 7/27/08) and treatment period (8/27/08 to 12/20/09) there were 6

dates where the source documents listed hemoglobin values but these were not specifically listed in the data listings for those dates. In two cases there was more than one assessment for hemoglobin done on the same date, and only one was captured in the CRF and data listings. The captured values recorded were not advantageous relative to the missed values. Review of the data listings shows that hemoglobin assessments were reported on dates just prior to and after the dates of missing assessments. It appears that the available hemoglobin values adjacent to the dates of missing values are similar in value and results to those available in the data listings. It is unclear why the sponsor omitted records for these hemoglobin values but the missing values should have no impact on study endpoint assessments.

OSI Reviewer's Note: These inspectional findings were discussed on several occasions with the review division Medical Officer, Martha Donoghue, to determine if they may have a significant impact on efficacy and safety study outcomes. Dr. Donoghue informed that these observations are of minimal concern since in all cases the subject had numerous blood draws and test results for the same tests but conducted either immediately before or after the dates of the "missed test result." In addition, on those dates where there were multiple identical blood draws for the same test, there was no indication that there was a bias in selecting which result to report for a given date. For these reasons, inspectional observations, related to these data points, should not significantly impact the reliability of safety or efficacy analyses in the application.

Consistent with the routine clinical investigator compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125166 STN-172 were compared. Data transcription deficiencies were noted. However, a Form FDA 483 was not issued because the data capture effort was conducted by the sponsor and not the site.

- c. **Assessment of data integrity:** With the exception of the observations noted above, the data for Dr. Gruppo's site, associated with Study C09-001r submitted to the Agency in support of BLA 125166 STN-172, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the final EIR.

9. Sponsor: Alexion Pharmaceuticals, Inc.

- a. **What was inspected:** The sponsor, Alexion Pharmaceuticals, Inc., was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. This inspection covered the sponsor responsibilities related to the following retrospective and prospective studies and clinical sites:

- C09-001r entitled “A Retrospective, Observational, Non-Interventional Trial to Assess Eculizumab Treatment Effect in Patients with Atypical Hemolytic Uremic Syndrome (aHUS)” (Retrospective)
- C08-002A/B entitled “An Open-Label, Multi-Center Controlled Clinical Trial of Eculizumab in Adult/Adolescent Patients with Plasma Therapy-Resistant Atypical Hemolytic-Uremic Syndrome (aHUS)”
- C08-003 A/B entitled “An Open-Label, Multi-Center Controlled Clinical Trial of Eculizumab in Adult/Adolescent Patients with Plasma Therapy-Sensitive Atypical Hemolytic-Uremic Syndrome (aHUS)”.

Protocol #	Clinical Investigator
C08-002A/B & C08-003A/B	Site #198-Christopher Legendre
C08-002A/B & C08-003A/B	Site #197-Yahsou Delmas
C08-002A/B & C08-003A/B	Site #196-Maryvonne Hourmant
C09-001r	Site #191-Veronique Baudouin
C09-001r	Site #192-Mary Alice Macher
C09-001r	Site #015-Jodi Smith
C09-001r	Site #013-Julius Sherwinter
C09-001r	Site #022-Ralph Gruppo

Note: The EIR was not available at the time this CIS was written. The EIR will be submitted to OSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Three studies were audited, 2 prospective studies, C08-002A/B and C08-003A/B, and a retrospective study, C09-001r. Review of the records found no evidence that the sponsor failed to maintain adequate oversight of the prospectively conducted clinical trails. Monitoring responsibilities for the prospective studies were contracted to a CRO. The sponsor reported that no clinical sites were closed due to serious noncompliance. The CRO and sponsor reviewed monitor reports and reportedly took steps to bring noncompliant sites into compliance by providing extra training or additional site visits. Site monitoring reports were not reviewed during this inspection because they are maintained at the CRO. Adverse events were managed by a CRO.

Regarding the retrospective study, CRFs were completed by monitors from a CRO that was contracted by the sponsor and the sponsor did not monitor the adequacy the performance of the CRO monitors. Case report forms for laboratory results were completed by the sponsor and there was no additional monitoring or auditing by the sponsor to assess the adequacy of this process.

This inspection was linked to the inspection of the eight clinical investigators listed above. FDA Investigators did not report any evidence of under-reporting of adverse events at these sites.

Reported PK data (Listing 16.2.6.6) was verified for all subjects listed in both the retrospective and prospective studies. In addition, PD data (Listing 16.2.6.7) was confirmed for all subjects in the prospective studies.

Consistent with the sponsor compliance program assessments, during the inspection data found in source documents and those measurements reported by the sponsor to the agency in BLA 125166 STN-172 were compared and verified. At the conclusion of the inspection no Form FDA 483 was issued. However, the inspectional findings identified a systemic lack of adequate monitoring of the retrospective study C09-001r. In spite of this failure to adequately monitor Study C09-001r the key efficacy and safety data generated for all of the subjects (5 of 30 subject; 18%) audited during FDA inspections was found to be reliable based on review of source records at the inspected clinical sites.

OSI Reviewer's Note: The sponsor's failure to adequately monitor a clinical study is typically listed as an inspection observation on a Form FDA 483; a violation of the pertinent GCP regulations. In this case, no Form FDA 483, Inspection Observations, was issued to the sponsor because the retrospective study, C09-001r, does not appear to meet the regulatory definition of a "clinical investigation" as defined in 21 CFR 312.3, thus the sponsor, may not be subject to regulations that require the sponsor ensure proper monitoring of an investigation (21 CFR 312.50).

- c. **Assessment of data integrity:** The data generated, as it pertains to Studies C08-002A/B & C08-003A/B and C09-001r was audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Notwithstanding the observations noted above for Study C09-001r, the data from this Sponsor submitted to the agency in support of BLA 125166 STN-172 appear reliable.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for eight clinical investigators' conduct of their respective studies; Dr. Christopher Legendre, Dr. Yahsou Delmas, Dr. Maryvonne Hourmant, Dr. Veronique Baudouin, Dr. Mary Alice Macher, Dr. Jodi Smith, Dr. Julius Sherwinter, and Dr. Ralph Gruppo, and the study sponsor, Alexion Pharmaceuticals, Inc., the study data collected appear reliable.

One clinical site inspected (Dr. Smith) was issued a Form FDA 483 citing inspectional observations however; the preliminary classification is No Action Indicated (NAI). It should be noted that the deficiencies reported for this site are actually attributable to the sponsor-specific

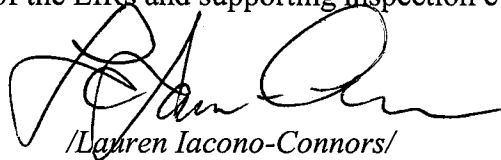
monitors and not the clinical investigator or the site as the CRO monitor was responsible for review of the subjects' source documents and completion of the CRF according to the investigational plan. For this reason the preliminary classification for Dr. Smith and for the remaining clinical investigator inspections is NAI.

It was determined during the inspection of Alexion Pharmaceuticals, Inc., that the sponsor did not adequately monitor the retrospective study C09-001r, however, for the reasons discussed in the previous section, the overall preliminary recommendation for the sponsor inspection is NAI. In regards to the sponsor inspection, the conduct and overall monitoring for both prospective studies appeared to be adequate. Regarding the retrospective study C09-001r, it should be noted that both the data collection effort and "monitoring" were done by the same persons, contractors or sponsor personnel, apparently at the same time. Therefore, there was not a separation of function between the staff charged with the collection/transcription of information found in source documents at the site/sponsor location, and the staff directed to conduct monitoring of this effort. While this is of concern, and was discussed extensively with the sponsor during the inspection, based on inspections of clinical investigator sites, the lack of adequate monitoring and observed deficiencies in data retrieval from source data that resulted, do not appear to impact the integrity of important efficacy and safety measurements critical to study interpretation.

The overall data in support of this application may be considered reliable based on available information.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

Follow-Up Actions: OSI will generate an inspection summary addendum if the conclusions change significantly upon final review of the EIRs and supporting inspection evidence and exhibits.



/Lauren Iacono-Connors/
Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:



/Jean Mulinde/
Jean Mulinde, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****Pre-decisional Agency Information*****

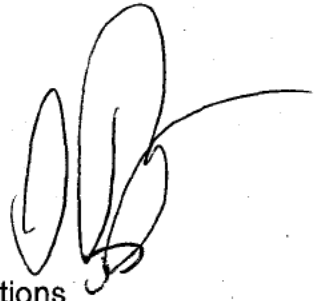
Memorandum

Date: 8/25/2011

To: Ebla Ali Ibrahim, Regulatory Project Manager
 Division of Hematology Products

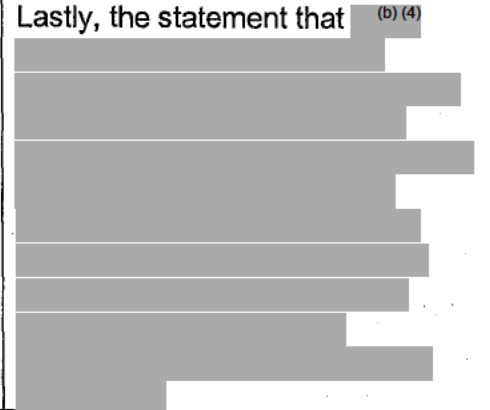
From: James Dvorsky, Regulatory Reviewer
 Division of Drug Marketing, Advertising, and Communications

Subject: Comments on draft labeling (Package Insert) for BLA 125166,
 Soliris (eculizumab)

8/25/11 

In response to your labeling consult request on April 29, 2011, we have reviewed the draft Package Insert for Soliris and offer the following comments. Note that these comments are based upon the 8-22-11 version of the label.

Package Insert Labeling:

Section	Statement	Comment
5.6 Laboratory Monitoring	aHUS 	Section 12.2 contains no  Section 14 contains no information  Lastly, the statement that 

6.1 Adverse Reactions	aHUS Table 4 (b) (4) (b) (4)	This sentence is not clear as to what the Table shows. As read, the table (b) (4) (b) (4) We recommend clarifying that, "Table (b) (4) summarizes all adverse events reported in at least 10%" and make a note that only "notable" or "important" events less than 10% are presented. It is also not clear that the Table presents each study independently and then provides a "total" column. We recommend revising the language to imply that adverse events are summarized for studies 1 and 2 separately and then a total column is provided.
6.1 Adverse Reactions	aHUS In aHUS Studies 1 and 2, 54% (20/37) of patients...	We recommend clarifying that this is "In aHUS Studies 1 and 2 combined..." The n value is presented but does not mitigate the notion that this result was observed in each trial separately.
14.2 aHUS	"Four of the five patients who required dialysis at study entry (b) (4) dialysis for the duration of Soliris treatment..."	It is not clear if these patients (b) (4) due to protocol mandated inclusion criteria or if a benefit of Soliris treatment was that these patients no longer needed dialysis. In the introduction paragraph for Study 1, it clearly states that enrolled patients were "without the need for chronic dialysis." This can be contradicting to the above statement that 5 patients needed dialysis.



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Pediatric and Maternal Health Staff Labeling Review

Date: August 8, 2011

Date Consulted: April 29, 2011

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Team Leader – Pediatric Team
Pediatric and Maternal Health Staff

Karen Feibus, MD, Team Leader – Maternal Health Team
Pediatric and Maternal Health Staff

Lisa Mathis, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Hematology Products (DHP)

Drug: Soliris (eculizumab) BLA 125166/172

Subject: Pregnancy, Nursing Mothers, and Pediatric Use Labeling

Materials Reviewed:

- Soliris labeling, submitted March 25, 2011 (edited by DHP)
- Response to Pregnancy Outcome Request with revised Pregnancy Labeling, submitted July 20, 2011

Consult Question: Please review the proposed Pregnancy, Nursing Mothers, and Pediatric Use subsections of Soliris labeling.

[Handwritten signatures and dates]
8/8/11
8/8/2011
8/8/11
8/8/11
(signing for Dr. Mathis as well in her absence)

INTRODUCTION

On March 25, 2011, Alexion Pharmaceuticals submitted a Supplemental Biologics Licensing Application (BLA 125166/172) for Soliris (eculizumab) the treatment of atypical Hemolytic Uremic Syndrome (aHUS) as a second indication. Soliris was approved for the treatment of patients with Paroxysmal Nocturnal Hemoglobinuria (PHN) to reduce hemolysis on March 16, 2007.

DHP consulted both the Pediatrics and Maternal Health teams of the Pediatric and Maternal Health Staff (PMHS) to review the proposed revised Pregnancy, Nursing Mothers, and Pediatric Use subsections of Soliris labeling.

BACKGROUND

Ecuzumab is a humanized monoclonal antibody which binds to human complement protein C5 and inhibits terminal complement activation. Ecuzumab is currently approved for the treatment of patients with Paroxysmal Nocturnal Hemoglobinuria (PHN) to reduce hemolysis. The Sponsor is seeking a second indication for the treatment of atypical Hemolytic Uremic Syndrome (aHUS). Paroxysmal Nocturnal Hemoglobinuria is a rare, acquired, potentially life-threatening disease of the blood characterized by complement-induced intravascular hemolytic anemia. Onset usually occurs between 20 to 40 years of age and affects approximately 1 to 5 per million people.¹ Atypical hemolytic-uremic syndrome is a rare, life-threatening condition characterized by three major features related to abnormal clotting: hemolytic anemia, thrombocytopenia, and kidney failure. Atypical HUS occurs more often in children under the age of 18 years than in adults. The incidence of aHUS in the U.S. is approximately 1 per 500,000 people.²

The main safety concern with the use of ecuzumab is an increased risk of meningococcal infections and other serious infections, particularly those caused by encapsulated bacterium, due to the inhibition of C5 activation. All patients receiving ecuzumab should receive a meningococcal vaccine at least two weeks prior to starting therapy. Children treated with Soliris should also receive vaccinations for the prevention of Streptococcus pneumoniae and Haemophilus influenza type b (Hib) infections according to Advisory Committee on Immunization Practices (ACIP) guidelines.

Pregnancy and Nursing Mothers Labeling

The Pregnancy and Nursing Mothers subsections of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus and/or infant. PMHS- maternal health labeling recommendations comply with current regulations but incorporate “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women when available, and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the

¹ <http://ghr.nlm.nih.gov/condition/paroxysmal-nocturnal-hemoglobinuria>

² <http://ghr.nlm.nih.gov/condition/atypical-hemolytic-uremic-syndrome>

available human and animal data, and when appropriate, clinical information that may affect patient management.

Pediatric Use Labeling

The Pediatric Use subsection should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted.

PROPOSED LABELING (with DHP edits)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

(b) (4)

(b) (4)

Soliris, a recombinant IgG molecule (humanized anti-C5 antibody) is expected to cross the placenta. Animal studies using mouse analogue of the Soliris molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and increased rates of dead and moribund offspring at doses 2-8 times the human dose. .

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 (b) (4) mothers exposed to the higher antibody does; 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.

8.3 Nursing Mothers

It is not known whether Soliris is excreted into human milk. IgG is excreted in human milk, so it is expected that Soliris will be present in human milk. However, published data suggest that (b) (4) do not enter the neonatal and infant circulation in substantial amounts.

Caution should be exercised when Soliris is administered to a nursing woman. The unknown risks to the infant from gastrointestinal or limited systemic exposure to Soliris should be weighed against the known benefits of (b) (4)

8.4 Pediatric Use

The safety and effectiveness of Soliris for the treatment of PNH in pediatric patients below the age of 18 years have not been established.

Three clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS included a total of 25 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 (b) (4)]

DISCUSSION AND CONCLUSIONS

Pregnancy Use

The Sponsor provided pregnancy outcome data on the use of eculizumab in 42 pregnancies. Forty one of the pregnancies occurred in women with PNH and one occurred in a woman with rheumatoid arthritis. Six of the pregnancies occurred in eculizumab clinical trials and 36 occurred postmarketing. The duration of eculizumab use during pregnancy varied. Increased doses of eculizumab were often required to block complement during later stages of these pregnancies. Twenty two of the pregnancies resulted in healthy infants, and three women had more than one pregnancy resulting in a healthy infant. Eleven pregnancies were unsuccessful with 5 spontaneous abortions, 3 elective abortions, 1 therapeutic abortion for intrauterine death, and 2 stillborns. One pregnancy resulted in maternal and fetal death due to complications of thrombosis and infection. No pregnancy outcome data are available for the use of eculizumab in women with aHUS.

PMHS recommends that a description of these limited eculizumab pregnancy outcome data be placed in labeling.

Nursing Mother Use

The Sponsor did not submit any data on the use of eculizumab during lactation. The Drug and Lactation Database (LactMed)³ provides the following data on the use of eculizumab in one lactating woman. This information is already incorporated in eculizumab labeling.

Limited information (one mother) indicates that maternal doses of eculizumab 900 mg daily produce undetectable levels in milk and would not be expected to cause any adverse effects in breastfed infants, especially if the infant is older than 2 months.

PMHS recommends that the terms “breast milk” and “breastfeeding” be changed to “human milk” and “human milk-feeding in labeling as these are the current preferred terms.

Pediatric Use

The Sponsor conducted two prospective, single-arm studies in adult and pediatric patients with aHUS, as well as a retrospective data collection study to capture information on adult and

³ <http://toxnet.nlm.nih.gov/cgi-bin/sis/search>

pediatric patients who received eculizumab for aHUS outside of the clinical trials. Six adolescent patients were enrolled in the prospective trials, and data from 4 adolescents were obtained through the retrospective study. No pediatric patients under the age of 12 years were enrolled in the prospective trials, and data from 15 pediatric patients less than 12 years of age (5 patients < 2 years of age (youngest patient, 2 months of age) and 10 patients 2 to < 12 years of age) were obtained through the retrospective study. Safety and effectiveness of eculizumab in children were similar to adults. Fever and infection were seen more frequently in pediatric patients less than 2 years of age; however, infections were not classified as serious.

As previously mentioned, eculizumab labeling contains a Boxed Warning regarding serious meningococcal infections and the need to vaccinate patients with a meningococcal vaccine at least two weeks prior to initiating eculizumab treatment and closely monitor patients for signs and symptoms of meningococcal infections. The recommendation for meningococcal vaccination may be problematic for younger infants that need to be treated with eculizumab as there are no meningococcal vaccines approved for this age group. The meningococcal conjugate vaccine (Menactra) is approved for use in infants 9 months of age and older. For prevention of other serious infections caused by encapsulated bacterium, the haemophilus B conjugate vaccine and the pneumococcal conjugate vaccine can be administered as early as 6 weeks of age. Young infants in the retrospective study were given prophylactic antibiotic treatment with eculizumab therapy. There are no data to support antibiotic prophylaxis without a known meningococcal exposure and prophylaxis in the absence of a known exposure could potentially lead to antibiotic resistance. Current ACIP guidelines should be followed for all patients. The Sponsor has proposed to follow pediatric patients treated with eculizumab and DHP plans to require an eculizumab pediatric registry for long-term patient follow-up as a postmarketing requirement.

The Pediatric Research Equity Act PREA (21 U.S.C. 355c) requires that all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration 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. Required pediatric studies under the PREA are not applicable for the aHUS indication, as orphan designation was granted for this indication.

PMHS LABELING RECOMMENDATIONS

The following labeling recommendations were discussed and agreed upon with DHP in a labeling held August 4, 2011.

_____USE IN SPECIFIC POPULATIONS_____

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

Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3).

Pediatric Use: PHN: safety and effectiveness not established; aHUS: safety and effectiveness similar to adult patients (8.4).

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There are no adequate and well-controlled studies of Soliris in pregnant women. Soliris, a recombinant IgG molecule (humanized anti-C5 antibody), is expected to cross the placenta.

Animal studies using a mouse analogue of the Soliris molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and moribund offspring at doses 2-8 times the human dose. Soliris should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

(b) (4)

(b) (4)

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.

8.3 Nursing Mothers

It is not known whether Soliris is excreted into human milk. IgG is excreted in human milk, so it is expected that Soliris will be present in human milk. However, published data suggest that antibodies in human milk do not enter the neonatal and infant circulation in substantial amounts. Caution should be exercised when Soliris is administered to a nursing woman. The unknown risks to the infant from gastrointestinal or limited systemic exposure to Soliris should be weighed against the known benefits of human milk-feeding.

8.4 Pediatric Use

The safety and effectiveness of Soliris for the treatment of PNH in pediatric patients below the age of 18 years have not been established.

Three clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS included a total of 25 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 *Dosage and Administration* (b) (4), *Adverse Reactions* (6.1), and *Clinical Studies* (14.2)].

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

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125166	NDA Supplement #:S- BLA STN # 172	Efficacy Supplement Type SE-
Proprietary Name: Soliris Established/Proper Name: Eculizumab Dosage Form: Sterile Parenteral Solution for Intravenous Infusion Strengths: 300 mg (10mg/mL)		
Applicant: Alexion Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: March 25, 2011 Date of Receipt: March 25, 2011 Date clock started after UN:		
PDUFA Goal Date: September 24, 2011		Action Goal Date (if different): N/A
Filing Date: May 24, 2011		Date of Filing Meeting: April 21, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): For the treatment of atypical Hemolytic Uremic Syndrome (aHUS).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): 11075

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: ☐ Not in arrears ☐ In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?					
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].					
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?					
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm					

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?				
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	✓			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			✓	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			✓	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	✓			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	✓			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”				
Field Copy Certification (NDAs/NDA efficacy supplements only) For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR) If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.	YES	NO	NA	Comment
			✓	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i>			✓	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.		✓		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			✓	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			✓	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			✓	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>	✓			
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			✓	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			✓	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			✓	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			✓	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		✓		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		✓		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 29, 2010 <i>If yes, distribute minutes before filing meeting</i>	✓			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		✓		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 21, 2011

BLA/NDA/Supp #: 125166/172

PROPRIETARY NAME: Soliris

ESTABLISHED/PROPER NAME: Eculizumab

DOSAGE FORM/STRENGTH: Sterile Parenteral Solution for Intravenous Infusion/ 300 mg (10mg/mL)

APPLICANT: Alexion Pharmaceutical, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

For the treatment of atypical Hemolytic Uremic Syndrome (aHUS)

BACKGROUND:

Alexion's approved eculizumab drug product Soliris[®] is for the treatment of patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) to reduce hemolysis. It was approved March 16, 2007. Alexion would like to include a second indication which is for the treatment of atypical Hemolytic Uremic Syndrome (aHUS).

An Orphan Drug Designation (ODD #09-2795) for eculizumab for the treatment for patients with aHUS was received on April 29, 2009.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ebla Ali Ibrahim	Y
	CPMS/TL:	Janet Jamison	Y
Cross-Discipline Team Leader (CDTL)	Ann Farrell		Y
Clinical	Reviewer:	Martha Donoghue	Y
	TL:	Ann Farrell	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		

OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Bahru Habtemariam	Y
	TL:	Julie Bullock	Y
Biostatistics	Reviewer:	Kyung Y Lee	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wei Chen	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Lixin Xu	Y
	TL:	Chana Fuchs	
Product Quality (CMC)	Reviewer:	Lixin Xu	Y
	TL:	Chana Fuchs	
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
505(b)(2) filing issues? If yes, list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments:	☐ Not Applicable
CLINICAL	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an original NME or BLA application, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	
• Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology (for sterile products)</u> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ebla Ali Ibrahim	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: sBLA 125166/Soliris (eculizumab)

PMR/PMC Description: Submit the final study report and datasets for the ongoing trial C10-003, entitled "An open-label, multi-center clinical trial of eculizumab in pediatric patients with atypical hemolytic uremic syndrome." This study will be amended to include pharmacokinetic, safety, and efficacy data from a minimum of 5 patients who are treated with eculizumab in each of the following age cohorts:

- 1 month to < 24 months
- 2 to < 5 years
- 5 to 12 years.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>11/15/2011</u>
	Study/Trial Completion:	<u>12/30/2013</u>
	Final Report Submission:	<u>09/01/2014</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Currently available efficacy and safety data are sufficient to support accelerated approval for a new indication, treatment of atypical hemolytic uremic syndrome, in pediatric patients. Accelerated approval for this indication is based on data derived from a pediatric subgroup in a small retrospective trial, supported by data from two prospective single arm trials in adults with the same diagnosis, in addition to pre- and post-marketing data from the treatment of adult patients with paroxysmal nocturnal hemoglobinuria.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The data from this ongoing trial will be used to confirm clinical benefit and further characterize safety and pharmacokinetics of eculizumab for the treatment of atypical hemolytic uremic syndrome in pediatric patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An open-label, multi-center clinical trial of eculizumab in pediatric patients with atypical hemolytic uremic syndrome. This study will be amended to include data from a minimum of 5 patients who are treated with eculizumab in each of the following age cohorts:

- 1 month to < 24 months
- 2 to < 5 years
- 5 to 12 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- x Does the study/clinical trial meet criteria for PMRs or PMCs?
- x Are the objectives clear from the description of the PMR/PMC?
- x Has the applicant adequately justified the choice of schedule milestone dates?
- x Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: sBLA 125166/Soliris (eculizumab)

PMR/PMC Description:

- Submit the final study report and datasets for the ongoing trial C10-004, entitled "An open-label, multi-center clinical trial of eculizumab in adult patients with atypical hemolytic uremic syndrome."

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>12/30/2012</u>
	Final Report Submission:	<u>09/01/2013</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Efficacy and safety data from two small prospective single arm trials in adults and one retrospective trial in adult and pediatric patients with atypical hemolytic syndrome, and pre- and post-marketing safety data from the treatment of adult patients with paroxysmal nocturnal hemoglobinuria, are sufficient to support accelerated approval of eculizumab in adult patients with atypical hemolytic uremic syndrome.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The data from this ongoing trial will be used to further characterize the safety and efficacy of eculizumab in this population. Due to the rarity of atypical hemolytic uremic syndrome, the three registration studies enrolled a total of 67 patients; therefore, the data from this ongoing study will add valuable information regarding the efficacy and safety of eculizumab in this population, and may provide information to better inform Soliris labeling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An open-label, multi-center clinical trial of eculizumab in adult patients with atypical hemolytic uremic syndrome.” This study will enroll a minimum of 30 patients.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: sBLA 125166/Soliris (eculizumab)

PMR Description: Evaluate the long-term safety of eculizumab by enrolling all patients with aHUS treated with eculizumab in a Soliris registry program and analyzing outcomes for a period of no less than five years. Submit periodic reports annually to the BLA including the specific items listed below. At the end of the five-year period, submit a final report to the BLA that describes the major safety findings from this registry, including the specific items listed below, and propose labeling changes as appropriate. The following data will be collected for each patient receiving eculizumab for the treatment of aHUS:

- Serious infections, defined as infections necessitating or prolonging hospitalization, or resulting in death. Alexion will collect follow-up information from these patients to assess the nature of the serious infection, the major features of the clinical course, and the survival status. We request expedited reporting (15 day telephone or facsimile Medwatch communication) for the occurrence of these serious infections.
- Malignancy, including the nature of the malignancy and the survival status of patients who develop a malignancy.
- Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among babies born to women exposed to eculizumab during the pregnancy.
- Survival
- Occurrence of stroke (yes/no)
- Requirement for renal transplant (yes/no)
- New dialysis requirement or increase in the frequency of dialysis (yes/no)
- aHUS exacerbation requiring plasma therapy (yes/no)
- Discontinuation (yes/no) and, if discontinued, the reason for discontinuation.

PMR Schedule Milestones:	Final Protocol Submission:	<u>11/2011</u>
	Interim Report Submission	<u>11/2012</u>
	Interim Report Submission	<u>11/2013</u>
	Interim Report Submission	<u>11/2014</u>
	Interim Report Submission	<u>11/2015</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Safety data from two prospective trials in adults and one retrospective trial in adult and pediatric patients with aHUS, and pre- and post-marketing safety data from the treatment of adult patients with paroxysmal nocturnal hemoglobinuria, are sufficient to support accelerated approval of eculizumab in adult and pediatric patients with aHUS.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Due to the rarity of atypical hemolytic uremic syndrome and lack of available therapy that has been rigorously studied, conducting a randomized trial to evaluate safety is not feasible. Longer term follow up of patient outcomes are necessary to better inform patients and physicians about the long-term safety of Soliris.

Because this is the first pediatric indication for Soliris, and because the immune function of young pediatric patients (particularly those less than 2-5 years of age) is different from that of adult patients, it is especially important to characterize the incidence and types of serious infections encountered in pediatric patients treated with Soliris.

Additionally, analysis of postmarketing data submitted by the applicant has indicated that approximately 47 patients (virtually all with PNH) developed a new malignancy (or premalignant condition, in the case of MDS), over the past four years. Although patients with PNH are known to be at increased risk for hematologic malignancies, a causal association between Soliris and secondary malignancies cannot be ruled out at this time. Because patients with aHUS, who are generally not thought to be at increased risk for the development of cancer, may have lifelong exposure to Soliris, it is important to capture information regarding the occurrence of malignancy in this population in order to enable a risk assessment in the future.

Patient survival, occurrence of stroke, requirement for renal transplant, new dialysis requirement, aHUS exacerbation requiring plasma therapy, and Soliris discontinuation are key variables reflecting long term patient outcome and Soliris safety that are relevant to the aHUS patient population.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A registry study to collect data to further characterize the long term safety of eculizumab for the treatment of atypical hemolytic uremic syndrome (aHUS).

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK

(signature line for BLAs)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125166s172

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Wednesday, September 21, 2011 1:06 PM
To: 'Lyons, Mary'
Subject: RE: Alexion proposed second sentence 09212011 1025.docx

Hello,

Please find below the division's proposal:

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

Please respond as soon as possible.

Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Wednesday, September 21, 2011 10:41 AM
To: Ali Ibrahim, Ebla
Cc: Lyons, Mary
Subject: Alexion proposed second sentence 09212011 1025.docx

Dear Ebla:

As requested in the teleconference this morning, please see attached Alexion's proposed options to the indication statement for your review.

We are available to discuss later today as needed.

Best regards,
Mary

Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410

Direct phone: (203) 271-8334
Fax: (203) 271-8191
email: lyonsm@alxn.com

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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Tuesday, September 20, 2011 1:26 PM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - Revised PMR
Importance: High
Attachments: BLA 125166_172 Revised PMR_Sept 20, 2011.doc

Hello Mary,

Per our conversation, please find attached the combined PMR #3 and PMR #4 to become PMR #3. The division decided to combine the collection of registry data for aHUS patient into a single PMR. Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Thursday, September 01, 2011 4:49 PM
To: Ali Ibrahim, Ebla
Cc: Lyons, Mary
Subject: RE: BLA 125166/172 - 4 Draft PMRs

Dear Ebla:

Attached please find Alexion's Response to the 4 PMRs provided in draft by the Division. No formal submission will be made.

Best regards,
Mary

*Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410*

Phone: (203) 271-8334
Fax: (203) 271-8191
Email: lyonasm@alxn.com

From: Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]
Sent: Friday, August 26, 2011 10:21 AM
To: Lyons, Mary
Subject: BLA 125166/172 - 4 Draft PMRs
Importance: High

Hello,

Please find attached a draft of the 4 PMRs that were discussed with you yesterday, Thursday, August 25, 2011. If possible, please respond by next Friday, September 2, 2011 with the PMR Schedule Milestone dates required. Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Tuesday, September 20, 2011 12:25 PM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - Additional Information Request - Soliris REMS documents
Importance: High

Hello.

Here are additional information request that needs to be addressed:

1. The Dosing & Administration Guide says the following:

(b) (4)

Change to: To enroll in the Soliris REMS and order Soliris, please call 1.888.SOLIRIS

How will you ensure prescribers who are accessing Soliris in an infusion center are enrolled in the REMS?

2. PROVIDE CLEAN COPIES OF ALL FINAL REMS MATERIALS- NO MARK UPS

3. The REMS Document and the following materials, which are part of the REMS should be appended to the REMS document

- (1) Soliris Patient Safety Card
- (2) Prescriber Introductory Letter and Enrollment Form
- (3) Patient Safety Brochure, Important Safety Information about Soliris
- (4) Prescriber Safety Brochure, Important Safety Information about Soliris
- (5) Dosing and Administration Guide
- (6) REMS website - screen shots The ISI should be part of the landing page of the REMS website

Please respond to all information requests as soon as possible, today or tomorrow.

Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
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10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

Tel: 301-796-3691

Fax: 301-796-9849

From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Monday, September 19, 2011 4:43 PM
To: Ali Ibrahim, Ebla
Cc: Lyons, Mary
Subject: Soliris REMS documents
Importance: High

Dear Ebla:

Attached, please find the REMS documents and appendices. As discussed, the PI and MedGuide are not final as yet. The wording in the REMS Appendices will be updated upon receiving the approved PI and MedGuide.

With respect to the website, the solirisREMS site has been updated in our internal staging server. The requested screenshots are included in the REMS (Appendix 6). Additionally, we have prepared a staging site for your review prior to approval. If you would like to browse this test site, please use this link: <http://solirisrems-staging/> The Medication Guide, the Prescribing Information, and all REMS materials links directly open the PDFs.

If you have any questions, please let me know.

Best regards,
Mary

*Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410*

*Direct phone: (203) 271-8334
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email: lyonsm@alxn.com*

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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Tuesday, September 20, 2011 12:19 PM
To: 'Lyons, Mary'
Subject: RE: Word versions of Med Guide and PI
Attachments: BLA 125166_172 PI FINAL 20 Sep 2011 redlined.doc

Hello,

The division accepts the 4 corrections you made to the PI .

The division's revision to the PI includes formatting and a statement, in track change, to the indication of aHUS, in both the Highlights and Full Prescribing sections. This statement was included due to the accelerated approval action. Please advise if you concur.

Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Monday, September 19, 2011 11:12 AM
To: Ali Ibrahim, Ebla
Cc: Lyons, Mary
Subject: Word versions of Med Guide and PI

As requested, here is the word version of the Med Guide as submitted to you on Friday, and the Word version of the PI with the 4 corrections mentioned in previous emails noted in track changes

Thanks
Mary

*Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.*

352 Knotter Drive
Cheshire, CT 06410

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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Tuesday, September 20, 2011 8:53 AM
To: 'Lyons, Mary'
Subject: Information Request - Soliris REMS documents
Importance: High

Good Morning Mary,

Please respond to the following information request:

1. How would you ensure prescribers who are accessing Soliris in an infusion center to be enrolled in the REMS?

2. We noted a discrepancy in the Patient Safety Card and should be consistent with the Med guide. It says

(b) (4)

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

(b) (4)

Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Monday, September 19, 2011 4:43 PM
To: Ali Ibrahim, Ebla
Cc: Lyons, Mary
Subject: Soliris REMS documents
Importance: High

Dear Ebla:

Attached, please find the REMS documents and appendices. As discussed, the PI and MedGuide are not final as yet. The wording in the REMS Appendices will be updated upon receiving the approved PI and MedGuide.

With respect to the website, the solirisREMS site has been updated in our internal staging server. The requested screenshots are included in the REMS (Appendix 6). Additionally, we have prepared a staging site for your review prior to approval. If you would like to browse this test site, please use this link: <http://solirisrems-staging/> The Medication Guide, the Prescribing Information, and all REMS materials links directly open the PDFs.

If you have any questions, please let me know.

Best regards,
Mary

*Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
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Cheshire, CT 06410*

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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Friday, September 16, 2011 8:14 AM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - FDA Revision - Med Guide

Importance: High

Attachments: BLA 125166_172 Med guide FDA Revision redline Sept 16, 2011.doc

Good Morning,

Please find attached the FDA's revision to the Medguide. A lot of the revision is formatting. Thank you.



BLA 125166_172
Med guide FDA R...

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
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10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Tuesday, September 13, 2011 9:30 AM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - FDA Revision - PI and Med guide

Importance: High

Attachments: BLA 125166_172 PI FDA Revision 13 Sept 2011-redline.doc; BLA 125166_172 Med guide FDA Revision 13 Sept 2011-redline.doc

Good Morning,

Please find attached FDA's revised PI and Med guide. Please respond by this Friday, September 16, 2011.

If there are any sections that you do not agree with, the division would like to have a telecon to discuss and come to an agreement, so that you can submit the final versions of the PI and the REMS documents which includes the Med guide this Friday.

Please also modify the REMS documents so that they are aligned with the final language of the PI and Med guide.



BLA 125166_172 PI BLA 125166_172
FDA Revision... Med guide FDA R...

Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
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Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Friday, September 09, 2011 12:27 PM
To: 'Lyons, Mary'
Subject: RE: BLA 125166/172 - Revised REMS Documents - (dedicated REMS webpage)
Importance: High
Attachments: 9-9-11 REMS Landing Page.doc

Good Morning,

Please find attached the FDA's revision to your REMS webpage.

The Soliris website should more clearly communicate that physician registration is required in order to obtain Soliris. We suggest that the first paragraph of the "Ordering Soliris" web page (entitled "How to order Soliris") include a sentence to inform physicians that the first step in the ordering process is to register through the REMS, along with a link to the REMS web page.

Please submit all final REMS documents as soon as possible.

Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
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Silver Spring, MD 20903*

Tel: 301-796-3691

Fax: 301-796-9849

From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Thursday, September 08, 2011 4:06 PM
To: Ali Ibrahim, Ebla
Cc: Lyons, Mary
Subject: RE: BLA 125166/172 - Revised REMS Documents - (dedicated REMS webpage)
Importance: High

Dear Ebla:

With respect to our response to item #5 last Friday, we have completed the development of the REMS-dedicated webpage as requested and in light of the additional specifics provided by you in your email on Tuesday, September 5.

The updates on <http://soliris.net> are now complete. To pilot the updated link behavior, please

1. Load this site page in your browser: <http://soliris.net/hcp/about-soliris>
2. Click the “**Soliris Safety, REMS**” link in the left navigation bar

The www.solirisREMS.com site will open in a new browser window with no ability to use the browser “Back” button to view marketing information.

If you have any additional questions, please do not hesitate to contact me.

Best regards,
Mary

*Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
Phone: (203) 271-8334
Fax: (203) 271-8191
Email: lyonsm@alxn.com*

From: Lyons, Mary
Sent: Friday, September 02, 2011 3:42 PM
To: 'Ali Ibrahim, Ebla'
Cc: Lyons, Mary
Subject: RE: BLA 125166/172 - Revised REMS Documents

Dear Ebla:

We agree with items # 1-4 below. With respect to item #5, we will develop a REMS-dedicated webpage as requested. The estimated time of implementation is 2 – 3 weeks.

Thank you.

Best regards,
Mary

*Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
Phone: (203) 271-8334
Fax: (203) 271-8191
Email: lyonsm@alxn.com*

From: Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]
Sent: Friday, September 02, 2011 12:27 PM
To: Lyons, Mary
Subject: BLA 125166/172 - Revised REMS Documents
Importance: High

Hello,

Please find attached the FDA's revision to the REMS documents. Please respond to the following comments below as soon as possible:

1. We have accepted the revised Patient Safety Card.
 2. We accepted the consolidation of the prescriber enrollment form and the introductory letter into a pre-addressed and stamped business format.
 3. We agreed with language that they placed into the documents.
 4. We acknowledged areas that are pending based on labeling negotiations.
 5. We are requesting that they comply with the FDA standard in placing REMS materials on the web (developing a REMS-dedicated webpage that does not include advertising etc).
- Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Tuesday, September 06, 2011 8:26 AM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - REMS

Good Morning,

The REMS materials, including the e-capable prescriber enrollment form, should be housed within a REMS-dedicated webpage that can be reached from www.Soliris.net. The REMS-dedicated webpage should be a final destination; that is, once in the REMS-dedicated webpage, the user should be able to access only REMS materials, and should not be able to access marketing materials. Screen shots of the REMS web landing page should be submitted, and the website landing page should be appended to the REMS. See our revision to REMS ETASU B to incorporate this standard.

The Soliris REMS landing page should include links to the Prescribing Information, Medication Guide and Important Safety Information at the top of the page.

There should also be clearly labeled tabs or separate hyperlinks prominently displayed on the webpage to the REMS materials (Prescriber Introductory Letter and Enrollment Form, Prescriber Safety Brochure, Soliris Patient Safety Card, Patient Safety Brochure, and Dosing and Administration Guide) that are part of the Soliris REMS program.

We recommend the following language as background information on the REMS landing page:

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks.

The goals of the Soliris REMS are:

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To (b) (4) educate Healthcare Professionals (HCP) and Patients (or Caregivers, or Legal Guardians) regarding:
 - o the increased risk of meningococcal infections with Soliris
 - o the early signs of invasive meningococcal infections, and
 - o the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections.

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Soliris with attached materials and the REMS Supporting Document. Provide a WORD document with tracked changes and a clean WORD version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate WORD documents.

Format Request: Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

Thank you.

*Abba Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
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10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

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Fax: 301-796-9849*

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Friday, September 02, 2011 12:27 PM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - Revised REMS Documents

Importance: High

Attachments: 9-2-11 from Alex Modified REMS aHUS 03262011_redlined draft.doc

Hello,

Please find attached the FDA's revision to the REMS documents. Please respond to the following comments below as soon as possible:

1. We have accepted the revised Patient Safety Card.
2. We accepted the consolidation of the prescriber enrollment form and the introductory letter into a pre-addressed and stamped business format.
3. We agreed with language that they placed into the documents.
4. We acknowledged areas that are pending based on labeling negotiations.
5. We are requesting that they comply with the FDA standard in placing REMS materials on the web (developing a REMS-dedicated webpage that does not include advertising etc).



9-2-11 from Alex
Modified REMS...

Thank you.

*bla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Monday, August 29, 2011 3:20 PM
To: 'Lyons, Mary'
Subject: RE: BLA 125166/172 - FDA Revised Package Insert (PI)

Hello,

Sorry to hear that your town has 80% power out. I did not have power outage and all we saw in my neighborhood was leaves down, not trees or branches down.

Please just email me the response by Friday. No need to submit it formally since discussions are still underway. Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
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Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Monday, August 29, 2011 2:46 PM
To: Ali Ibrahim, Ebla
Subject: RE: BLA 125166/172 - FDA Revised Package Insert (PI)

Hi Ebla:

For this response, is an email version acceptable on Friday? Since discussions are still underway, would an official sequence be necessary?

Our publishers have a holiday schedule and may not be able to process on Friday.

Please let me know.

Thanks
Mary

PS how did you fare with the hurricane? My town has 80% power out and expect 4 more days til restored.

Alexion just got their power restored.

From: Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]
Sent: Friday, August 26, 2011 10:03 AM
To: Lyons, Mary
Subject: BLA 125166/172 - FDA Revised Package Insert (PI)
Importance: High

Good Morning,

Please find attached the PI with the agency's revision in track change. Please accept the changes acceptable to you and leave your edits in track change. Please respond by next Friday, September 2, 2011 or sooner. Please note that there might be more revisions to sections under discussion.

I will forward you the Med guide as soon as DRISK includes their revision. Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Friday, August 26, 2011 10:21 AM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - 4 Draft PMRs

Importance: High

Attachments: BLA 125166_172 4 PMRs_26 August 2011.doc

Hello,

Please find attached a draft of the 4 PMRs that were discussed with you yesterday, Thursday, August 25, 2011. If possible, please respond by next Friday, September 2, 2011 with the PMR Schedule Milestone dates required. Thank you.



BLA 125166_172 4
PMRs_26 Augus...

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
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10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

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Fax: 301-796-9849*

4 draft PMRs

1. Submit the final study report and datasets for the ongoing trial C10-003, entitled "An open-label, multi-center clinical trial of eculizumab in pediatric patients with atypical hemolytic uremic syndrome." This study will be amended to include pharmacokinetic, efficacy and safety data from a minimum of 5 patients who are treated with eculizumab in each of the following age cohorts:

- 1 month to < 23 months
- 2 to < 5 years
- 5 to 12 years.

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

2. Submit the final study report and datasets for the ongoing trial C10-004, entitled "An open-label, multi-center clinical trial of eculizumab in adult patients with atypical hemolytic uremic syndrome."

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

3. Develop and implement a registry to collect data to further characterize the long term efficacy of eculizumab for the treatment of atypical hemolytic uremic syndrome (aHUS). The following data will be collected for a time period of no less than five years for each patients receiving eculizumab for the treatment aHUS:

- Patient death (yes/no)
- Stroke (yes/no)
- Requirement for renal transplant (yes/no)
- New dialysis requirement or increase in the frequency of dialysis (yes/no)
- aHUS exacerbation requiring plasma therapy (yes/no)
- Discontinuation of eculizumab (yes/no) and, if discontinued, the reason for discontinuation.

Submit periodic reports annually to the BLA. At the end of the five year period, submit a final study report to the BLA that describes the major efficacy findings, including the specific items listed above.

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

4. To evaluate long-term safety of eculizumab in patients with aHUS by analyzing outcomes in the Soliris Safety Registry for a period of no less than five years. At the end of the five year period, submit a final study report to the BLA that describes the major safety findings from this registry, including the specific items listed below, and propose labeling changes as appropriate. The following data will be collected for each patient receiving eculizumab for the treatment aHUS:

- Serious infections, defined as infections necessitating or prolonging hospitalization, or resulting in death. Alexion will collect follow-up information from these patients to assess the nature of the serious infection, the major features of the clinical course, and the survival status. Expedited reporting (15 day telephone or facsimile Medwatch communication) will be provided for the occurrence of these serious infections.
- Malignancy, including the nature of the malignancy and the survival status of patients who develop a malignancy.
- Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among babies born to women exposed to eculizumab during the pregnancy.
- Thrombotic events, including the nature of the event, the clinical outcome, as well as the anticoagulant management prior to and after the event.

PMR Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Friday, August 26, 2011 10:03 AM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - FDA Revised Package Insert (PI)

Importance: High

Attachments: 26 August 2011 USPI plr redlined.doc

Good Morning,

Please find attached the PI with the agency's revision in track change. Please accept the changes acceptable to you and leave your edits in track change. Please respond by next Friday, September 2, 2011 or sooner. Please note that there might be more revisions to sections under discussion.

I will forward you the Med guide as soon as DRISK includes their revision. Thank you.



26 August 2011
USPI plr redlin...

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Friday, August 19, 2011 7:57 PM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - FDA Comments and Revision to the REMS and REMS Supporting Document

Importance: High

Attachments: CL+8-19-11 draft mu REMS aHUS 03192011_FDA_markup.doc

Hello Mary Lyons,

The comments below are based on FDA's initial review of your REMS modification proposal for Soliris. Please note that additional changes might be needed as the REMS modification undergoes additional review within the FDA. Please make the requested changes and return within 7 days (by next week Friday, August 26, 2011).

Based upon draft modification of the Soliris PI to remove discontinuation hemolysis and other serious infections from the adverse event sections, we have made revisions to the REMS and REMS Supporting Document showing the necessary changes. We made additional changes to the REMS for consistency with the current draft labeling.

The REMS materials (Soliris Patient Safety Card, Prescriber Introductory Letter, Patient Safety Brochure, *Important Safety Information about Soliris*, Prescriber Safety Brochure, *Important Safety Information about Soliris*, Prescriber Enrollment Form, Dosing and Administration Guide) should be attached directly to the REMS document. The materials may be included in the REMS Supporting Document as well.

We drafted suggested changes to the survey instruments to remove discontinuation hemolysis and other serious infections from the surveys, and to incorporate labeling changes from your draft Soliris labeling submitted to the FDA with the application for the expanded indication. Submit the methodology and survey instrument(s) for review at least 90 days before the next evaluation is conducted. Submit both methods and instruments together.

We note that your product website does not state that enrollment in the REMS is required to prescribe Soliris. This information should be included on the Soliris website.

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Soliris with attached materials and the REMS Supporting Document. Provide a WORD document with tracked changes and a clean WORD version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate WORD documents.

Format Request: Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

Please find attached the FDA's revision to the REMS and REMS Supporting Document.

Thank you.



CL+8-19-11 draft
mu REMS aHUS ...

Ebla Ali Ibrahim, MS

*Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
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Silver Spring, MD 20903*

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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
nt: Tuesday, July 26, 2011 10:59 AM
io: 'Lyons, Mary'
Subject: BLA 125166/172 - Information Request

Good Morning,

Please email me a word version of the REMS and REMS Supporting Document. Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
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Fax: 301-796-9849*

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Wednesday, July 06, 2011 2:30 PM
To: 'Lyons, Mary'
Subject: RESPONSE - Information Request - BLA 125166/172

Hello,

Question #4 is also pertained to malignancy events. Page 25 of the US Periodic Report for Soliris (dated May 27, 2011) contains the following paragraph:

6.3.7.3. Malignancy

There were 40 reported cases of malignancy during this review period (Table 8). Thirty seven case cases are considered as not related for the following reasons: pre-existing condition, progression of disease, or the **mechanism of action of Soliris**. Three cases lacked sufficient clinical information to determine if there was a causal relationship to Soliris and the pathophysiology of cancer.

Thank you.

*Ebla Ali Ibrahim, MS
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From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Tuesday, July 05, 2011 5:06 PM
To: Ali Ibrahim, Ebla
Cc: Lyons, Mary
Subject: RE: Information Request - BLA 125166/172

Dear Ebla:

Would you please clarify / confirm whether Request #4 below is a separate request that is not related to

malignancy and is related to the Periodic Report information whereas Requests #1-3 are specifically related to malignancy.

Thank you.

Mary Lyons

*Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
Phone: (203) 271-8334
Fax: (203) 271-8191
Email: lyonsm@alxn.com*

From: Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]
Sent: Monday, June 27, 2011 3:33 PM
To: Lyons, Mary
Subject: Information Request - BLA 125166/172

Hello Mary Lyons,

The clinical reviewer for sBLA 125166 requests the following information to assess the risk of secondary malignancy with eculizumab therapy.

1. A listing of secondary malignancies reported over the past 3-5 years, broken down by year.
2. The number of patients treated during each year.
3. For each report of malignancy, please specify the type of malignancy, and whether this represents a new diagnosis, recurrence, or disease progression. In addition, please provide the indication for eculizumab therapy, duration of therapy prior to diagnosis of malignancy, and patient outcome.
4. The most recent US Periodic Report for Soliris (dated May 26, 2011) indicates that some cases were attributed to the "mechanism of action of Soliris." Please elaborate on the meaning of this statement.

Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Friday, July 01, 2011 1:12 PM
To: 'Lyons, Mary'
Subject: Additional Information Request - BLA 125166/172

Hello,

Please provide the following information to facilitate our understanding of the procedure that was used for data collection and monitoring of the quality of data collection for Study C09-001r. If you have questions or require clarification regarding this request, please feel free to contact us.

1. A copy of the Contract Agreement and Charter (if available) between Alexion and the CRO that was contracted to go to clinical sites, review source records and transcribe study specific data/results to the study CRFs.
2. A description of training provided to the CRO by Alexion related to the task of data collection and transcription at each clinical site. If available, copies of training materials would be ideal.
3. A copy of the monitoring plan used to ensure that data was consistently and accurately captured from source documents onto the CRFs.

Thank you.

*Ebla Ali Ibrahim, MS
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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Wednesday, June 29, 2011 12:02 PM
To: 'Lyons, Mary'
Subject: Information Request - BLA 125166/172

Hello,

The Pediatric and Maternal Health Staff would like Alexion to update the Packet Insert (PI) subsection 8.1 Pregnancy, with pregnancy outcome data from their PNH and aHUS clinical trials, along with any additional published pregnancy outcome data. Published literature is available on limited pregnancy outcome data and the literature reports that you followed several pregnancies that occurred in the clinical trials with eculizumab. We are aware that the data is limited; however, the conditions are rare and the limited data can be used to better inform pregnancy labeling.

Thank you.

*Ebla Ali Ibrahim, MS
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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Monday, June 27, 2011 3:33 PM
To: 'Lyons, Mary'
Subject: Information Request - BLA 125166/172

Hello Mary Lyons,

The clinical reviewer for sBLA 125166 requests the following information to assess the risk of secondary malignancy with eculizumab therapy.

1. A listing of secondary malignancies reported over the past 3-5 years, broken down by year.
2. The number of patients treated during each year.
3. For each report of malignancy, please specify the type of malignancy, and whether this represents a new diagnosis, recurrence, or disease progression. In addition, please provide the indication for eculizumab therapy, duration of therapy prior to diagnosis of malignancy, and patient outcome.
4. The most recent US Periodic Report for Soliris (dated May 26, 2011) indicates that some cases were attributed to the "mechanism of action of Soliris." Please elaborate on the meaning of this statement.

Thank you.

*Ebla Ali Ibrahim, MS
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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Thursday, June 09, 2011 10:25 AM
To: 'Lyons, Mary'
Subject: RE: Response to INfo Requests on June 8, 2011

Good Morning,

Please submit your responses as soon as they are available. Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
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*Tel: 301-796-3691
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From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Thursday, June 09, 2011 10:15 AM
To: Ali Ibrahim, Ebla
Cc: Lyons, Mary
Subject: Response to INfo Requests on June 8, 2011

Dear Ebla:

We received three separate emails containing Information Requests yesterday. Would you prefer the responses submitted individually or can they be bundled as it becomes available?

Please advise.

Thanks
Mary

*Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
Phone: (203) 271-8334
Fax: (203) 271-8191
Email: lyonsm@alxn.com*

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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Wednesday, June 08, 2011 3:39 PM
To: 'Lyons, Mary'
Subject: BLA 125166/172 Additional Information Request - Clinical

Hello,

Please respond as soon as possible to the following:

Please provide an analysis of patients who experienced an aHUS exacerbation while being treated with eculizumab in Studies C08-002, C08-003, and C09-001r. If this analysis is in the clinical study reports, please provide information regarding the location of this analysis. For each patient who experienced a breakthrough exacerbation, please provide information regarding the trigger for the exacerbation, whether the patient was being treated according to the proper dose and schedule recommended for eculizumab prior to the exacerbation, the study day during which the exacerbation occurred, the duration and outcome of the exacerbation, the interventions required to treat the exacerbation, and whether or not eculizumab therapy was continued during and after the resolution of the exacerbation.

Thank you.

*Ebla Ali Ibrahim, MS
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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
nt: Wednesday, June 08, 2011 12:44 PM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - Information Request - Clinical/Stats
Importance: High

Hello,

Please respond to the following as soon as possible:

Please clarify the definition of hematologic normalization used in each study.

In the clinical study report for the retrospective study, hematologic normalization is defined as "Normalization of platelet count and LDH levels in patients who had abnormal platelet counts at baseline or immediately prior to baseline. The LDH criterion was waved if no LDH measurement was reported during eculizumab therapy." According to the SAP, baseline is defined as the last available measurement taken prior to the first dose.

However, patient 019-025 is listed as a patient who achieved hematologic normalization, although her platelet count was $153 \times 10^9/L$ the day prior to the start of eculizumab and $218 \times 10^9/L$ on Day 0. LDH was abnormal. Are patients eligible to achieve hematologic normalization if LDH is abnormal and platelet counts are normal at baseline?

For Study C08-003 A/B, the majority of patients who were categorized as achieving hematologic normalization actually maintained normal hematologic parameters, rather than achieving normalization, since most had normal parameters upon entry, correct?

Regarding the ahuseff.xpt dataset provided on May 17, 2011:

1. Please explain the criteria for choice of the EOS target day in the PLTCHGD field and the GFRCHGD fields.
2. Are the calculations for duration in the HEMNRMDR, TMADR, TMAEFDR fields in this dataset based upon the last available lab prior to data cut-off that meets the prespecified criteria for each patient?
3. What are the criteria for eGFR improvement required for the GFRIMP field? There are some patients who appeared to have over $20 \text{ ml/min}/1.73 \text{ m}^2$ improvement (e.g., patient 121-029 in the retrospective study and 2-140-001 in study 002), that were not considered to have eGFR improvement. Is this because it was for too short of a duration? Conversely, there were a few patients in the retrospective study who had a change from baseline that was less than 20, and one patient with a negative change from baseline, who were assigned a "1" in the GFRIMP field.
4. Is the GFRCHGD field, what is meant by the "EOS Target DAY for eGFR"? Is this the day of the last eGFR measurement prior to data cut-off that met criteria for improvement in EGFR, or is it just the last eGFR measurement prior to data cut-off?

If GFRCHGBL is not the value used to determine whether a patient was considered to have an improvement in eGFR, can you provide a listing for each patient who was considered to have an improvement in eGFR that includes:

the amount of improvement, the beginning and end study days during which the minimum required improvement was observed and the duration of improvement?

.ank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
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Fax: 301-796-9849*

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Wednesday, June 08, 2011 11:55 AM
To: 'Lyons, Mary'
Subject: RE: BLA 125166/172 - PLEASE CLARIFY: Additional Information Request

Good Morning,

Here is an update to request #2 below:

Regarding request number # 2 (originally sent on 6/1/2011) , we are looking for pooled PK dataset based on LABPK dataset. Please also add individual clearance estimates from final population PK model. Please send within 3 working days.

Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
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*Tel: 301-796-3691
Fax: 301-796-9849*

From: Ali Ibrahim, Ebla
Sent: Monday, June 06, 2011 3:30 PM
To: 'Lyons, Mary'
Subject: RE: BLA 125166/172 - PLEASE CLARIFY: Additional Information Request
Importance: High

Hello,

1. Request #1 is fulfilled by the submission dated June 3, 2011 (Seq # 0225).
2. Regarding request number #2, we are looking for pooled PK dataset based on LABPK dataset.

Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research*

Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
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Fax: 301-796-9849

From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Wednesday, June 01, 2011 1:32 PM
To: Ali Ibrahim, Ebla
Cc: Lyons, Mary
Subject: RE: BLA 125166/172 - PLEASE CLARIFY: Additional Information Request
Importance: High

Dear Ebla:

With respect to today's emailed Information Request, would you please clarify the following:

1. Please correct subject level dataset sets submitted on 5/18/2011 by updating the unique patient id to be a combination of patient id and study number, which are typically 12 digits (e.g., C08-002-xxx-xxx).
 - A proposal was emailed to you on May 18, but the formal submission regarding the derived datasets was made on May 24, 2011 (Seq 0219). Are the derived datasets submitted in Sequence 0219 the ones that you are requesting that we update with a combination patient ID and study number?

2. Please submit a separate a pooled PK dataset consisting of the following:
 - At minimum, provide unique patient id, study id, eculizumab dose, eculizumab concentration, PK measurement day, visit number.
 - Do you want a pooled dataset based on the PK modeling datasets (submitted as Sequence 0222 submitted on May 27, 2011)
 - OR a pooled dataset based on the LABPK dataset

Thank you for clarifying.
Best regards
Mary

Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
Phone: (203) 271-8334
Fax: (203) 271-8191
Email: lyonsm@alxn.com

From: Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]
Sent: Wednesday, June 01, 2011 10:39 AM
To: Lyons, Mary
Subject: BLA 125166/172 - Additional Information Request

Good Morning,

Please respond within 3 working days to the information request below:

1. Please correct subject level dataset sets submitted on 5/18/2011 by updating the unique patient id to be a combination of patient id and study number, which are typically 12 digits (e.g., C08-002-xxx-xxx).
2. Please submit a separate a pooled PK dataset consisting of the following:
 - At minimum, provide unique patient id, study id, eculizumab dose, eculizumab concentration, PK measurement day, visit number.

Thank you.

*Ebla Ali Ibrahim, MS
Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
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10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Tuesday, June 07, 2011 10:13 AM
To: 'Lyons, Mary'
Subject: RE: BLA 125166/172 - PLEASE CLARIFY: Additional Information Request

Good Morning,

Please submit it as a formal submission. You can email it to me as well. Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Tuesday, June 07, 2011 10:02 AM
To: Ali Ibrahim, Ebla
Subject: RE: BLA 125166/172 - PLEASE CLARIFY: Additional Information Request
Importance: High

Dear Ebla

Thanks you for your email. We are in the process of preparing the revised response to #2. Please advise if we can send via email or a formal submission is needed.

Thank you.

Mary

*Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
Phone: (203) 271-8334
Fax: (203) 271-8191
Email: lyonsm@alxn.com*

From: Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]
Sent: Monday, June 06, 2011 3:30 PM
To: Lyons, Mary
Subject: RE: BLA 125166/172 - PLEASE CLARIFY: Additional Information Request
Importance: High

Hello,

1. Request #1 is fulfilled by the submission dated June 3, 2011 (Seq # 0225).
2. Regarding request number #2, we are looking for pooled PK dataset based on LABPK dataset.

Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Wednesday, June 01, 2011 1:32 PM
To: Ali Ibrahim, Ebla
Cc: Lyons, Mary
Subject: RE: BLA 125166/172 - PLEASE CLARIFY: Additional Information Request
Importance: High

Dear Ebla:

With respect to today's emailed Information Request, would you please clarify the following:

1. Please correct subject level dataset sets submitted on 5/18/2011 by updating the unique patient id to be a combination of patient id and study number, which are typically 12 digits (e.g., C08-002-xxx-xxx).
 - A proposal was emailed to you on May 18, but the formal submission regarding the derived datasets was made on May 24, 2011 (Seq 0219). Are the derived datasets submitted in Sequence 0219 the ones that you are requesting that we update with a combination patient ID and study number?
2. Please submit a separate a pooled PK dataset consisting of the following:
 - At minimum, provide unique patient id, study id, eculizumab dose, eculizumab concentration, PK measurement day, visit number.
 - Do you want a pooled dataset based on the PK modeling datasets (submitted as Sequence 0222 submitted on May 27, 2011)

- OR a pooled dataset based on the LABPK dataset

Thank you for clarifying.

Best regards

Mary

*Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
Phone: (203) 271-8334
Fax: (203) 271-8191
Email: lyonsm@alxn.com*

From: Ali Ibrahim, Ebla [<mailto:Ebla.Ali-Ibrahim@fda.hhs.gov>]

Sent: Wednesday, June 01, 2011 10:39 AM

To: Lyons, Mary

Subject: BLA 125166/172 - Additional Information Request

Good Morning,

Please respond within 3 working days to the information request below:

1. Please correct subject level dataset sets submitted on 5/18/2011 by updating the unique patient id to be a combination of patient id and study number, which are typically 12 digits (e.g., C08-002-xxx-xxx).
2. Please submit a separate a pooled PK dataset consisting of the following:
 - At minimum, provide unique patient id, study id, eculizumab dose, eculizumab concentration, PK measurement day, visit number.

Thank you.

*Ebla Ali Ibrahim, MS
Regulatory Health Project Manager
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Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Monday, June 06, 2011 3:30 PM
To: 'Lyons, Mary'
Subject: RE: BLA 125166/172 - PLEASE CLARIFY: Additional Information Request
Importance: High

Hello,

1. Request #1 is fulfilled by the submission dated June 3, 2011 (Seq # 0225).
2. Regarding request number #2, we are looking for pooled PK dataset based on LABPK dataset.

Thank you.

*Ebla Ali Ibrahim, MS
Senior Regulatory Health Project Manager
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*Tel: 301-796-3691
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From: Lyons, Mary [mailto:LyonsM@alxn.com]
Sent: Wednesday, June 01, 2011 1:32 PM
To: Ali Ibrahim, Ebla
Cc: Lyons, Mary
Subject: RE: BLA 125166/172 - PLEASE CLARIFY: Additional Information Request
Importance: High

Dear Ebla:

With respect to today's emailed Information Request, would you please clarify the following:

1. Please correct subject level dataset sets submitted on 5/18/2011 by updating the unique patient id to be a combination of patient id and study number, which are typically 12 digits (e.g., C08-002-xxx-xxx).
 - A proposal was emailed to you on May 18, but the formal submission regarding the derived datasets was made on May 24, 2011 (Seq 0219). Are the derived datasets submitted in Sequence 0219 the ones that you are requesting that we update with a combination patient ID and study number?
2. Please submit a separate a pooled PK dataset consisting of the following:
 - At minimum, provide unique patient id, study id, eculizumab dose, eculizumab concentration, PK measurement day, visit number.

- Do you want a pooled dataset based on the PK modeling datasets (submitted as Sequence 0222 submitted on May 27, 2011)
- OR a pooled dataset based on the LABPK dataset

Thank you for clarifying.

Best regards

Mary

*Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
Phone: (203) 271-8334
Fax: (203) 271-8191
Email: lyonsm@alxn.com*

From: Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]
Sent: Wednesday, June 01, 2011 10:39 AM
To: Lyons, Mary
Subject: BLA 125166/172 - Additional Information Request

Good Morning,

Please respond within 3 working days to the information request below:

1. Please correct subject level dataset sets submitted on 5/18/2011 by updating the unique patient id to be a combination of patient id and study number, which are typically 12 digits (e.g., C08-002-xxx-xxx).
2. Please submit a separate a pooled PK dataset consisting of the following:
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Thank you.

*Ebla Ali Ibrahim, MS
Regulatory Health Project Manager
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recipient, any use, copying, disclosure, dissemination or distribution is strictly prohibited. If there is any reason to believe you are not the intended recipient, please notify the sender immediately by return email and delete this communication and destroy all copies. Thank you.

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Wednesday, June 01, 2011 10:39 AM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - Additional Information Request

Good Morning,

Please respond within 3 working days to the information request below:

1. Please correct subject level dataset sets submitted on 5/18/2011 by updating the unique patient id to be a combination of patient id and study number, which are typically 12 digits (e.g., C08-002-xxx-xxx).
2. Please submit a separate a pooled PK dataset consisting of the following:
 - At minimum, provide unique patient id, study id, ecuzumab dose, ecuzumab concentration, PK measurement day, visit number.

Thank you.

*Ebla Ali Ibrahim, MS
Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
1903 New Hampshire Avenue, Rm 2159
Ber Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
Sent: Monday, May 16, 2011 3:38 PM
To: 'Lyons, Mary'
Subject: Additional Information Request

Importance: High

Hello,

Here are information requests from Stats and Clinical. Please respond as soon as possible:

Stats:

1. Please provide the derived efficacy datasets for c08-002 and c08-003. The derived efficacy datasets should include all the efficacy endpoints per subject in the separate column including all the important demographic and sensitivity analyses variables. For example of the platelet count endpoint, platelet counts for baseline, week 1-week 26, locf values, and other important demographic values per subject should be in the separate column in the derived efficacy dataset. The efficacy analyses should be performed without merging many datasets. If there are discrepancies between Alexion and FDA reviewer's results, it really takes time to figure it out.

Clinical:

2. Please submit a copy of the protocol for the ongoing pediatric aHUS study to the BLA?

Thank you.

*Ebla Ali Ibrahim, MS
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Fax: 301-796-9849*

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
nt: Friday, May 13, 2011 5:13 PM
To: 'Lyons, Mary'
Subject: RE: Clinical Pharm Information Request

Hello,

Please find below a revision to question 1. The revision is in blue below:

1. Please provide integrated efficacy and safety datasets as specified below by combining results of studies C08-002, C08-003, and C09-001r together. The efficacy and safety datasets should be separate. Please send all datasets in sas transport format (*.xpt).

Efficacy:

The efficacy dataset should include the following variables: study id, unique patient ID, age, weight, gender, eculizumab induction dose ,eculizumab maintenance dose, baseline platelet count, platelet count change from baseline, platelet count ≥ 150 , hematologic normalization, complete TMA response, TMA event-free status, TMA intervention, Quality of Life mean change from baseline, decrease creatinine > 25 , CDK improvement by > 1 stage, eGFR improvement ≥ 15 , eGFR change from baseline, time to response (response=TMA event free, platelet normalization, creatinine improvement, GFR improvement $\geq 1,5$ and complete TMA response). Please not that some of the variables should be dichotomous indicator variables (e.g. 1 or 0), while others are continuous variable.

Safety:

The safety dataset should include the following variables: study id, unique patient ID, age, weight, gender, eculizumab dose, infection (presence or absence), hypertension event, and other grade 3 or 4 adverse events that occur at rate greater than $> 5\%$.

Thank you.

*Ebla Ali Ibrahim, MS
Regulatory Health Project Manager
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Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

From: Ali Ibrahim, Ebla
Sent: Wednesday, May 11, 2011 5:03 PM
To: 'Lyons, Mary'
Subject: Clinical Pharm Information Request

Hello Mary Lyons,

ase submit the requested datasets by May 18, 2011:

1. Please provide integrated efficacy and safety datasets as specified below by combining results of studies

C08-002, C08-003, and C09-001r together. The efficacy and safety datasets should be separate. Please send all datasets in sas transport format (*.xpt).

Efficacy:

The efficacy dataset should include the following variables: study id, unique patient ID, age, weight, gender, eculizumab dose, baseline platelet count, platelet count change from baseline, platelet count ≥ 150 , hematologic normalization, complete TMA response, TMA event-free status, TMA intervention, Quality of Life mean change from baseline, decrease creatinine > 25 , CDK improvement by > 1 stage, eGFR improvement ≥ 15 , eGFR change from baseline, time to response (response=TMA event free, platelet normalization, creatinine improvement, GFR improvement $\geq 1,5$ and complete TMA response). Please note that some of the variables should be dichotomous indicator variables (e.g. 1 or 0), while others are continuous variable.

Safety:

The safety dataset should include the following variables: study id, unique patient ID, age, weight, gender, eculizumab dose, infection (presence or absence), hypertension event, and other grade 3 or 4 adverse events that occur at rate greater than $> 5\%$.

2. Please provide protocol of on-going pediatric study.

Thank you.

*Ebla Ali Ibrahim, MS
Regulatory Health Project Manager
Division of Hematology Products
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Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
nt: Wednesday, May 11, 2011 5:03 PM
To: 'Lyons, Mary'
Subject: Clinical Pharm Information Request

Hello Mary Lyons,

Please submit the requested datasets by May 18, 2011:

1. Please provide integrated efficacy and safety datasets as specified below by combining results of studies C08-002, C08-003, and C09-001r together. The efficacy and safety datasets should be separate. Please send all datasets in sas transport format (*.xpt).

Efficacy:

The efficacy dataset should include the following variables: study id, unique patient ID, age, weight, gender, eculizumab dose, baseline platelet count, platelet count change from baseline, platelet count ≥ 150 , hematologic normalization, complete TMA response, TMA event-free status, TMA intervention, Quality of Life mean change from baseline, decrease creatinine > 25 , CDK improvement by > 1 stage, eGFR improvement ≥ 15 , eGFR change from baseline, time to response (response=TMA event free, platelet normalization, creatinine improvement, GFR improvement $\geq 1,5$ and complete TMA response). Please not that some of the variables should be dichotomous indicator variables (e.g. 1 or 0), while others are continuous variable.

Safety:

The safety dataset should include the following variables: study id, unique patient ID, age, weight, gender, eculizumab dose, infection (presence or absence), hypertension event, and other grade 3 or 4 adverse events that occur at rate greater than $> 5\%$.

2. Please provide protocol of on-going pediatric study.

I thank you.

*Ebla Ali Ibrahim, MS
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Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

*Tel: 301-796-3691
Fax: 301-796-9849*

Ali Ibrahim, Ebla

From: Ali Ibrahim, Ebla
nt: Wednesday, April 27, 2011 12:31 PM
To: 'Lyons, Mary'
Subject: BLA 125166/172 - Information Request

Hello Mary Lyon,

The clinical reviewer for sBLA 125166/172 requests the following information:

1. Please provide the location of the certified source documentation that served as the basis for the case report forms for Study C09-001r. We may request that copies of these certified source documents be submitted to the sBLA for review.
2. Please provide a detailed explanation of how subjects and investigator sites were identified for inclusion in Study C09-001r. The Statistical Analysis Plan and Study Report for this study indicate that the treatment centers were identified by Alexion based on the number and location of aHUS patients treated with eculizumab between 2007 and 2009, but do not explain how Alexion was aware that these patients were treated with eculizumab.
3. Please confirm that the contact information for the following investigators are current and correct:

Site 198: Christophe Legendre - Hôpital Necker-Enfants Malades, Service de Transplantation Rénale adulte et Soins Intensifs 149, rue de Sèvres, 75743 Paris Cedex 15 Ph. +33.1.44.49.54.32
Fax.+33.1.44.49.54.30

Site 197: Yahsou Delmas - CHU Pellegrin, Département de Néphrologie, Unité d'hémodialyse, Place Amélie Raba Léon, 33076 Bordeaux cedex Ph. +33.5.56.79.55.37, Fax.+33.5.56.79.60.32

Site 196: Maryvonne Hourmant - Hôtel Dieu-CHU de Nantes, Service de, Néphrologie et d'Immunologie Clinique, 30 boulevard Jean Monnet. 44093 Nantes Cedex 1 – FRANCE Ph. 33.2.40.08.74.45, Fax.33.2.40.08.74.48

Site 191: Veronique Baudouin -Hôpital Robert Debrém, Service Nephrologie, 48, Boulevard Sérurier, 75935 Paris Cedex 19 Phone: 33.01.400.32455

Site 192: Mary Alice Macher - AP-DP Hôpital Robert Debré, Service Nephrologie, 48, Boulevard Sérurier, 75935 Paris Cedex 19 Ph. 01.400.32396 Fax. 01.400.32468

Site 015: Jodi Smith - Seattle Children's, 4800 Sand Point Way NE, P.O. Box 50020, Seattle, WA 98105 Ph. 206.987.2524 Fax. 206.987.2636

Site 018: John Friedewald - Northwestern University, Feinberg School of Medicine, 675 N. Saint. Clair Street, Suite 1900, Chicago, IL 60611 Ph. 312.695.0338 Fax. 312.695.9194

Site 044: Craig Langman - Children's Memorial Hospital, 2300 Childrens Plaza #37, Chicago, IL 60614 Ph. 773.327.3930 Fax. 773.327.3937

Please submit your responses to your supplement 125166/172 as soon as possible.

Thank you.

*Ebla Ali Ibrahim, MS
Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
103 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903*

Tel: 301-796-3691

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125166 Supplement Number: 172 NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Hematology PDUFA Goal Date: September 24, 2011 Stamp Date: 3/25/2011

Proprietary Name: Soliris

Established/Generic Name: Eculizumab

Dosage Form: Sterile Parenteral Solution for Intravenous Infusion

Applicant/Sponsor: Alexion Pharmaceuticals

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) Treatment of patients with PNH to reduce hemolysis
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of patients with aHUS to inhibit complement0mediated thrombotic microangiopathy

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

justification):

‡ Not feasible:

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
☐ Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐ All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Ebla Ali Ibrahim  Apr 21, 2011

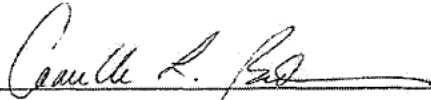
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

3. DEBARMENT CERTIFICATION

Alexion Pharmaceuticals, Inc. does hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

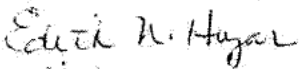


Camille L. Bedrosian, M.D.
Senior Vice President, Chief Medical Officer

16 Feb 2011

Date

Signed before me - this 16th day of February, 2011


Notary

my commission expires 7/31/12



IND 11075

MEETING MINUTES

Alexion Pharmaceuticals, Inc.
Attention: Mary F. Lyons, RAC
Senior Manager, Regulatory Affairs
352 Knotter Drive
Cheshire, CT 06410

Dear Ms. Lyons:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Eculizumab.

We also refer to the meeting between representatives of your firm and the FDA on July 29, 2010. The purpose of the meeting was to discuss the potential filing for registration to add atypical Hemolytic Uremic Syndrome (aHUS) to the indication statement.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3691.

Sincerely,

Ebla Ali Ibrahim, M.S.
Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-sBLA

Meeting Date and Time: July 29, 2010, 3:00 PM – 4:00 PM
Meeting Location: FDA White Oak Campus, Bldg 22, Rm 1315

Application Number: IND 11075
Product Name: Eculizumab
Proposed Indication: For patients with atypical Hemolytic Uremic Syndrome (aHUS).

Sponsor/Applicant Name: Alexion Pharmaceuticals

Meeting Chair: Edvardas Kamiskas, M.D.
Meeting Recorder: Ebla Ali Ibrahim, M.S.

FDA ATTENDEES

Division of Hematology Products (DHP)

Edvardas Kaminskas, M.D., Acting Deputy Director
Kathy Robie Suh, M.D, Ph.D., Medical Team Leader
Andrew Dmytrijuk, M.D., Medical Officer
Ashkan Emadi, M.D., Medical Officer
Diane Leaman, Regulatory Safety Project Manager
Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager

Office of Pharmaceutical Science, Office of Biological Products, Division of Monoclonal Antibodies

Lixin Xu, M.D., Ph.D., Product Quality Reviewer

Office of Clinical Pharmacology (OCP)

Julie Bullock, Pharm.D., Clinical Pharmacology Team Leader
Aakanksha Khandelwal, Ph.D., Clinical Pharmacologist

IND 11075
Meeting Minutes
Type B
July 29, 2010

Office of Oncology Drug Products
Division of Hematology Products

Office of Biostatistics, Division of Biometrics V

Qing Xu, Ph.D., Statistician

SPONSOR ATTENDEES

Camille L. Bedrosian, M.D., Senior VP, Global Clinical Dev. & Chief Medical Officer

Claude Nicaise, M.D., Senior VP, Strategic Development & Global Regulatory Affairs

Stephen Squinto, Ph.D., Executive VP and Head of Research and Development

Rebecca Velez, Pharm.D., Director, Project Management

Masayo Ogawa, M.D, Senior Medical Director, Clinical Development

Elizabeth Sullivan, Associate Director, Project Management

Mary F. Lyons, RAC, Senior Manager, Regulatory Affairs

BACKGROUND:

The indication for Eculizumab (approved product under the trade name Soliris) is for treatment of patients with Paroxysmal Nocturnal Hemoglobinuria (PNH). The proposed indication for Eculizumab is for patients with atypical Hemolytic Uremic Syndrome (aHUS). Alexion Pharmaceuticals requested a type B meeting with the Division of Hematology Products (DHP) to discuss the potential filing to add atypical Hemolytic Uremic Syndrome (aHUS) to the indication. On July 27, 2010, DHP sent Alexion preliminary responses to the questions contained in the background package dated June 28, 2010.

MEETING OBJECTIVE:

The meeting objective was to reach an agreement with the Agency regarding the potential filing for registration to add atypical Hemolytic Uremic Syndrome (aHUS) as a second indication.

DISCUSSION:

Alexion gave a presentation of their studies (see slides attached) explaining the reason for the design and endpoint.

The Division asked Alexion, considering that aHUS is not common, how they were able to enroll patients so quickly in the studies. Alexion stated that the studies took place in multiple centers and that when patients called them, the patients were either directed to a center or a center was opened for them close by.

Alexion clarified the dosing regimen used in studies C08-002A/B and C08-003A/B. The induction phase consisted of 900 mg eculizumab QW x 4 doses followed by 1200 mg during Week 5. The maintenance phase consisted of 1200 mg eculizumab Q 14 days. Alexion acknowledged that this dose was higher than that used in the PNH patient population and stated that they would provide the dose rationale based on pharmacokinetic modeling in the sBLA submission.

Alexion asked the Division for guidance for efficacy and endpoint. The Division advised Alexion that the FDA has been very reluctant to approve drugs on the basis of laboratory values; rather, a favorable result must be demonstrated in a clinically meaningful endpoint. A change in platelet count alone would not be an adequate primary endpoint. The Division advised Alexion to consider changing the primary endpoint at least for study C08-002A/B from a response in platelet count to an endpoint which would be more clinically meaningful such as a composite endpoint that includes hematologic normalization (i.e., platelet count and LDH) and renal function response. The Division suggested that a composite endpoint of hematological response and plasma therapy-free status may be an appropriate primary endpoint for study C08-003A/B. The division advised Alexion to develop the endpoint with community physician assistance. Alexion said they were considering such endpoints.

Alexion stated that for the studies each patient would act as their own control (i.e., endpoints would be assessed as change from baseline). The Division asked if Alexion could develop a historical control at each site. Alexion responded that they plan to submit historical control data from the literature

DECISIONS (AGREEMENTS) REACHED:

- Alexion and the Division agreed that primary endpoints based on just the platelet count response are not adequate to show the efficacy of eculizumab for the treatment of aHUS.

ACTION ITEMS:

- Alexion will submit historic information in a literature review that they are preparing, data collected for each patient from the beginning to the end of the study. Alexion will reconsider the primary endpoints which will be analyzed for the registration studies.

ATTACHMENTS AND HANDOUTS:

See attached FDA's final Comments/Responses to the specific questions asked by Alexion Pharmaceuticals, Inc.

Specific Questions and FDA Responses:

1. *The preliminary data from two ongoing studies presented in this document provides evidence of safety and efficacy of eculizumab for the treatment of patients with aHUS. These data will be updated with a minimum of 6 months follow-up. Do you agree that these data can support the filing of the sBLA in support of the indication for the treatment of aHUS?*

FDA Response:

Possibly. We have the following comments:

- **We need to discuss the efficacy endpoints of these studies. The primary endpoint in Study C08-002A/B was a change in platelet count and Study C08-003A/B had the platelet count as part of the primary endpoint. We are concerned that an improvement in platelet count as the major assessment of effectiveness of the drug may not adequately reflect clinically meaningful efficacy in aHUS. Although both studies showed an apparent significant increase in platelet count from baseline, only 10/17 patients in Study C08-002A/B and 2/20 patients in Study C08-003A/B had an improvement in chronic kidney disease stage. The primary efficacy endpoint should provide a clear measure of clinical benefit.**
- **We note that the studies used a single-arm, open label study design, which does not allow for a direct comparison of safety and efficacy of Eculizumab (e.g., compared to a standard of care such as plasma therapy). To allow quantitative assessment of efficacy it may be possible to utilize a historical control, such as well-documented disease, treatment and response history of enrolled patients prior to study entry or disease assessments, course, treatments and outcomes for aHUS patients treated at the study centers prior to initiation of your studies.**
- **The number of aHUS patients studied (total of 37) is small. You should provide justification for the small number of patients proposed for the sBLA, especially considering the relatively short duration of study enrollment.**
- **Treatment duration was limited in the two studies. Due to the need for prolonged therapy in aHUS, study data up to 1 year is desirable to support the safety and efficacy of Eculizumab for the treatment of aHUS.**

2. *A REMS for Soliris is approved. Should Alexion provide an updated REMS at the time of submission?*

FDA Response:

Yes, you should provide updated REMS.

3. *The 120 day safety update will include all safety data (AE, SAE, death and discontinuations) of the two ongoing studies. Alexion also propose to include an update of the pediatric study and the new study in adult patients. Is this proposal acceptable?*

FDA Response:

The 120 safety update should contain updated safety information for all patients exposed to Eculizumab from all available sources. The update should include data from pre-marketing clinical studies and postmarketing experience, as well as any other safety data obtained for patients exposed to Eculizumab.

4. *A Table of Contents for the sBLA is included in this document. The submission will follow the requirement for an eCTD. Do you have any comment on content or format?*

FDA Response:

The proposal is acceptable but please provide the following:

- a. **All SAS programs that were used to create all of the efficacy and safety tables and figures included in the main test portion of the CSR. Please also provide all necessary macros and SAS utility programs. All programs should be thoroughly commented and have passed Sponsor's validation procedures.**
- **An index of the SAS programs that were used to produce all of the efficacy and safety tables and figures in the main test portion of the CSR.**
 - **Ensure the SAS dataset file name are consistent with those in the SAS programs that call them, so that the Agency can run the programs smoothly to verify the results/figures/tables reported in the submission.**
 - **Annotations for all efficacy and safety tables and figures should be included in the main test portion of the CSR. The annotations should indicate which analysis dataset variables were used to produce the table or figure.**

- b. **Datasets should have one and only one unique subject ID for each patient among all trials. One record should contain all data for one patient.**
 - c. **Variables used in the define datasets should be the same for all datasets so that sets can be combined or sorted as needed for cross study evaluations.(i.e., one definition, well-annotated, per one variable)**
5. *Data listings datasets will be prepared and will be available at the time of submission. Should the listings be included in Module 5 and fully referenced as part of the eCTD format?*

FDA Response:

Yes, the listing should be included in Module 5 and fully referenced as part of the eCTD format.

6. *Case report forms for the deaths and discontinuations will be provided. Is there any recommendation regarding the format for such submission?*

FDA Response:

Because of the small number of patients in both aHUS studies (C08-002A/B and C08-003A/B), you should submit case report forms for all 37 patients that were enrolled in these studies for review in the sBLA. In addition, all information available for patients in study C09-001r should be submitted.

7. *Alexion intends to include a section 2.7.2. to describe PK and PD data in the aHUS population. Section 2.7.2 will present how initial experience in PNH allowed the development of a PK/PD model in which complement inhibition is consistently demonstrated with eculizumab concentration above 35 mcg/ml and how this model was used to develop the dosing recommendation in the whole aHUS population. PK and PD data and relationship to model from the prospective trials as well as from the retrospective trial will be discussed. Is this proposal acceptable?*

FDA Response:

While the proposal to include the above information in section 2.7.2 of the eCTD is acceptable we would also like you to include the following:

- a. **An evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK (pharmacokinetics) of eculizumab in the aHUS patient population. Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in**

identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.

- b. Provide all concentration-time and derived PK parameter datasets for all aHUS studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with range as appropriate.
- c. Provide a table listing of patients with renal or hepatic impairment who have received eculizumab, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.
- d. We encourage you to refer to the following pharmacometric data and models submission guidelines
(<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm>):
All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Additional Comments

Clinical:

1. The initial sBLA submission should include full follow-up (at least 6 months) for all patients in both studies, i.e., for the 17 patients in C08-002A/B and all 20 patients in C08-003A/B and not just 16 of 20 patients in C08-003A/B as stated in the current background package.

- 2. Provide an explanation of why 9 patients did not enroll in the retrospective data collection for patients treated with Eculizumab outside of these 2 trials.**

Clinical Pharmacology:

- 3. Please provide data on the effect of eculizumab on the QT/QTc interval in the sBLA. If this data is not available, please identify the clinical protocol(s) that will incorporate an adequate ECG monitoring plan to characterize impact on QTc in the sBLA and provide a post-marketing commitment, including a timeline for key milestones. The protocol(s) should be submitted to the IND for FDA review.**
- 4. Provide an update on the immunogenicity of eculizumab in the aHUS patient population.**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-11075	GI-1	ALEXION PHARMACEUTICA LS INC	Eculizumab

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

/s/

EBLA ALI IBRAHIM
08/27/2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 125166	NDA Supplement # BLA STN # 172	If NDA, Efficacy Supplement Type:
Proprietary Name: Soliris Established/Proper Name: Eculizumab Dosage Form: Sterile Parenteral Solution for Intravenous Infusion		Applicant: Alexion Pharmaceuticals, Inc Agent for Applicant (if applicable):
RPM: Ebla Ali Ibrahim		Division: Division of Hematology Products
NDA: NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)		505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s): Provide a brief explanation of how this product is different from the listed drug. If no listed drug, explain. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ Other (explain) <u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☐ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.
❖ Actions		
• Proposed action • User Fee Goal Date is <u>September 24, 2011</u>		☒ AP ☐ TA ☐ CR
• Previous actions (<i>specify type and date for each action taken</i>)		☒ None

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics ² Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rx-to-OTC full switch ☐ Rolling Review ☐ Rx-to-OTC partial switch ☐ Orphan drug designation ☐ Direct-to-OTC NDAs: Subpart H BLAs: Subpart E ☐ Accelerated approval (21 CFR 314.510) ☒ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 314.520) ☐ Restricted distribution (21 CFR 601.42) Subpart I Subpart H ☐ Approval based on animal studies ☐ Approval based on animal studies ☐ Submitted in response to a PMR REMS: ☒ MedGuide ☐ Submitted in response to a PMC ☒ Communication Plan ☐ Submitted in response to a Pediatric Written Request ☐ ETASU ☐ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☒ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other BURST

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If yes, NDA/BLA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire _____
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i>	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes No

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If “Yes,” skip to question (4) below. If “No,” continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If “No,” continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “No,” continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	September 23, 2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Accelerated Approval, September 23, 2011
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	April 6, 2011
• Example of class labeling, if applicable	N/A

³ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	March 25, 2011
• Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	N/A
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	N/A
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☒ DMEPA August 29, 2011 ☒ DRISK September 9, 2011 ☒ DDMAC August 29, 25, 2011 ☐ SEALD ☐ CSS ☒ Other reviews PMHS - August 8, 2011
Administrative / Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review⁴/Memo of Filing Meeting) (<i>indicate date of each review</i>)	April 21, 2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Designation</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	☒ Verified, statement is acceptable
❖ Outgoing communications <i>(letters (except action letters), emails, faxes, telecons)</i>	September 21, September 20, September 20, September 20, September 20, September 16, September 13, September 9, September 6, August 29, August 26, August 26, August 19, July 26, July 6, July 1, June 29, June 27, June 9, June 8, June 8, June 8, June 7, June 6, June 1, May 16, May 13, May 11, April 27,
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	☒ No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☒ N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	☐ No mtg July 29, 2011
• EOP2 meeting <i>(indicate date of mtg)</i>	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☒ None
Division Director Summary Review <i>(indicate date for each review)</i>	☐ None September 15, 2011
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☒ None
PMR/PMC Development Templates <i>(indicate total number)</i>	☐ None 3
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	August 31, 2011
• Clinical review(s) <i>(indicate date for each review)</i>	August 31, 2011
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	See Clinical Review page 29
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	☒ Not applicable

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	March 25, 2011 ☐ None DRISK Final Review - September 22, 2011; DRISK Interim REMS Review #2 - September 2, 2011; #1 - August 19, 2011
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	☐ None requested August 26, 2011
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☐ None August 24, 2011
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None August 24, 2011
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None August 24, 2011
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None September 1, 2011
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☐ None September 1, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	☒ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ None
• Supervisory Review(s) (<i>indicate date for each review</i>)	☒ None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☒ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☒ None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None August 30, 2011
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	☐ None August 30, 2011
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	August 30, 2011. See Product Quality Review on page 3
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.