CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166

MEDICAL REVIEW

Date: March 15, 2007
From: Karen D. Weiss, M.D. KW
Subject: Office level memorandum: BLA STN 125166/0 Eculizumab (Soliris™), Alexion
To: File

The Division of Medical Imaging and Hematology Products and members of the review team for the above referenced BLA recommend an approval action. I concur with this recommendation. Below is a brief summary of the application with attention to major points of discussion surrounding the product labeling.

Alexion Pharmaceuticals, Inc. submitted the above referenced Biological License Application (BLA) on September 15, 2006. The product, Eculizumab (Soliris™), is a monoclonal antibody directed against complement C5. The product was studied for its efficacy and safety in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH), a rare disease characterized by a deficiency in terminal complement inhibitor. The hallmark of this disease is chronic intravascular hemolysis secondary to complement-mediated lysis. Manifestations of the disease are related to the hemolysis and include anemia, fatigue, transfusion requirements, and thromboses. The disease manifestations and their severity vary from patient to patient.

Soliris™ inhibits the actions of terminal complement by blocking C5 activation. This mechanism provides the rationale for its use in PNH as well as the major safety concern of serious meningococcal disease, discussed below. In this BLA, the major evidence for efficacy and safety derive from TRIUMPH, a randomized, placebo controlled trial in patients with transfusion-dependent PNH ($\geq$ 4 transfusions/month). A total of 87 patients were randomized 1:1 to Soliris™ or placebo for 26 weeks. Treatment was administered intravenously as follows: 600 mg q 7 days X 4 weeks, then 900 mg for dose 5, then 900 mg q 14 days thereafter. This dose/regimen chosen was based on pK and pD modeling data to identify the concentrations of eculizumab needed to block terminal C5 activation. These data were derived from pk/pd studies in several different patient populations. The specific regimen for PNH was derived from a study in 40 PNH patients in which serum LDH, a marker of hemolysis, was markedly reduced by week 1 and sustained at week 26.

The major efficacy outcomes were measures of hemolysis. The co-primary endpoints were hemoglobin stabilization rates and avoidance of RBC transfusions. Secondary outcomes included other measures of hemolysis and fatigue. Patients randomized to Soliris™ had significant improvements in all primary and secondary outcomes compared to placebo treated patients. The most frequent adverse reactions relative to placebo treated patients were constitutional symptoms – headache, nausea, back pain, and naso-pharyngitis. There were no differences between groups in rates of serious adverse reactions and no severe infusion reactions.

Additional data were derived from a single arm trial (SHEPHERD) in which 97 patients who required at least one RBC transfusion in the past 12 months received Soliris™ at the

same dose and schedule as in TRIUMPH, but for 52 weeks. The hemolysis-related parameters at the end of the study were similar to the results in TRIUMPH.

Patients who had enrolled in and completed initial Soliris™ studies were eligible for an extension study. In the extension study, 187 patients continued with Soliris™ at the same dose and schedule as above. The exposure ranged from 10 months to 54 months. Patients maintained improvements in signs and symptoms of hemolysis.

The major safety concern, closely related to the mechanism of action of the drug, is serious infection from encapsulated bacteria, primarily meningococcal infections. All PNH patients were required to be vaccinated with meningococcal vaccine prior to receiving Soliris™. Despite this, 2 of 196 PNH patients still developed a serious meningococcal infection; fortunately, no one died as a result of their infection. The high degree of concern about this serious safety issue and ability to minimize risk through vaccination are described in various sections of the product labeling, including the boxed warning, contra-indication, Medication Guide, and specific risk minimization program that will involve initial and ongoing patient and provider education.

A theoretical safety concern is the risk of excessive thrombosis from abrupt Soliris™ discontinuation. This situation could arise because Soliris™ treatment reduces the hemolysis and therefore results in expansion of PNH cells. These expanded cells would still be susceptible to complement-mediated hemolysis. In the clinical trial experience, no patient had evidence of enhanced or exaggerated hemolysis. The package insert includes a warning/precaution about the potential for this type of event.

A major point of contention with the sponsor was whether and if so, what data to include in the PI about the effect of Soliris™ on thromboses. In all the clinical studies, approximately 50-60% of the patients were on anticoagulants during the study; some because of known thromboses, others as prophylaxis. In TRIUMPH, there was 1 thrombotic event in the placebo arm and 0 in Soliris™ arm. The sponsor argued that the event rate was so low, and study duration and small sample size prohibited that study from being able to show an effect. They proposed to draw evidence of the effectiveness of Soliris™ on thromboses from the extension trial by comparing rates/per patient years prior to and while on treatment. However, FDA concluded that these types of observational data were not sufficient [redacted] decreased thromboses and moreover, the PI needed to include a warning/precaution not to alter anticoagulant management as a result of Soliris™. The PI does include a statement that in the extension trial, there were fewer thrombotic events on Soliris™ than during the same period of time prior to Soliris™ along with caveats about inability to conclude the effects of anticoagulant withdrawal. The sponsor has agreed to conduct as part of a PMC a study to evaluate the withdrawal of anticoagulation while on Soliris™.

In addition, the sponsor will evaluate patients in a registry, and periodically submit results periodically, and assess the impact of their risk minimization plan on occurrence of serious meningococcal infection.

DIVISION DIRECTOR'S REVIEW MEMORANDUM

BLA:	125166
DRUG:	Eculizumab injection, solution for intravenous use
TRADENAME:	Soliris®
FORMULATION:	300 mg single-use vials, containing 30 mL of 10 mg/mL sterile, preservative-free soluation
ROUTE:	Intravenous administration as an infusion over 35 minutes
DOSE:	600 mg every seven days for the first four weeks, followed by 900 mg for the fifth dose seven days later, then 900 mg every 14 days thereafter
SPONSOR:	Alexion Pharmaceuticals, Inc.
SUBMITTED:	September 15, 2006
PDUFA DUE DATE:	March 17, 2007
DD MEMO COMPLETED:	March 10, 2007
DD MEMO PREPARERS:	Dwaine Rieves, MD, Acting Division Director Division of Medical Imaging and Hematology Products

SPONSOR'S PROPOSED INDICATION:

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

RELATED DRUGS:

Soliris is the first FDA-approved product specifically indicated for treatment of PNH.

RELATED REVIEWS:

Clinical:	Andrew Dmytrijuk, M.D.; Kathy Robie Suh, M.D., Ph.D.
Statistics:	Yuan Richard Chen, Ph.D, Jyoti Zalkikar, Ph.D.
Chemistry:	Michelle Jessen, Ph.D., Joseph Kutza, Ph.D., Kurt Brorson, Ph.D.
Microbiology:	Benda Uratani, Ph.D., Patricia Hughes, Ph.D.
Pharm-toxicology:	Siham Biade, Ph.D., Adebayo Laniyonu, Ph.D.
Clin Pharmacology:	Ike Lee, Ph.D, Hong Zhao, Ph.D.
Project Manager:	Florence Moore, RN, MSN, RAC
SEALD Reviewers:	Melissa Furness and Laurie Burke (Study endpoint and label development)
Advisory Committee:	None

RECOMMENDED REGULATORY ACTIONS:

1) Licensure of Soliris for the treatment of PNH to reduce hemolysis:

PNH is a very rare (estimated prevalence of no more than 500 patients in the United States) condition that manifests with:

- intravascular hemolysis
- thrombosis
- bone marrow hypoplasia or aplasia

Patients with PNH may manifest none or all three of these major clinical problems although red blood cell (RBC) hemolysis is the most common presentation of the condition. RBC hemolysis is the only condition that was shown, in clinical studies, to be altered by Soliris therapy.

RBC hemolysis in PNH patients occurs through the development of a clonal population of RBC that are exceptionally susceptible to lysis by complement. These cells are referred to as "PNH cells." The development of this clone is due to a somatic mutation in marrow cells. Hence, the clonal population affects not only RBC but also white blood cells and other cells derived from the marrow. The complement-mediated hemolysis results in anemia that may require RBC transfusions.

The other major clinical manifestations of PNH, thrombosis and marrow aplasia/hypoplasia, account for most of the mortality in the condition and the extent, if any, to which these problems mechanistically relate to hemolysis is unknown. Only about one-half of all PNH patients will ever experience a thrombotic event and even fewer will experience marrow aplasia. The rarity of these events, combined with the overall rarity of PNH, may have contributed to the sponsor's inability to establish Soliris treatment effects upon thrombotic complications and marrow hypoplasia/aplasia.

Soliris is a humanized monoclonal antibody that inhibits C5, a key complement component protein. Administration of Soliris results in a form of drug-induced complement deficiency which, in PNH patients, allows PNH cells to survive such that this clonal population expands in the blood and increases the blood's total content of RBC.

The sponsor submitted data from one adequate and well controlled clinical study that provided substantial evidence of Soliris safety and efficacy in the treatment of hemolysis among adult PNH patients. Overall, safety data were obtained from 196 PNH patients exposed to Soliris. The most important safety finding was the occurrence of *Nesseria meningitidis* septicemia among two PNH patients. Meningococcal sepsis or meningitis is the major risk for use of Soliris. These safety concerns are addressed in product labeling and the sponsor's use of a risk minimization plan that focuses on education and voluntary compliance with meningococcal vaccination.

All review teams concur with the decision for licensure of Soliris. The submitted safety and efficacy data did not present unique challenges in data review or interpretation and the findings were regarded as sufficiently persuasive to preclude the need for a discussion at an Advisory Committee.

2) Requirement of the sponsor to conduct post-marketing studies and to submit additional information:

The sponsor has agreed to provide no less than five years of follow-up clinical data regarding Soliris usage, including any Soliris usage among pediatric patients and pregnant patients. This information will be obtained from a special registry to be maintained by the sponsor. Additionally, follow-up safety data obtained in this registry will include the detection of malignancies, serious infections and antibody formation. No controlled clinical studies are required as post-marketing commitments.

An additional post-marketing commitment pertains to the submission of a final risk minimization document that describes the "Soliris Guardian Program," the sponsor's risk

management program that was submitted in draft form during the review (it was contingent, in part, upon finalization of labeling).

Multiple chemistry, manufacturing and controls (CMC) items were also components of post-marketing commitments (PMC).

3) Approval of the trade name, Soliris®

This recommendation is consistent with that of the FDA Office of Drug Safety/Division of Medication Errors and Technical Support.

4) No Pediatric Research Equity Act (PREA) of 2003 expectations:

Soliris has an Orphan Product designation. Hence, PREA does not directly apply to the licensure. Nevertheless, the sponsor's post-marketing registry is designed to obtain outcome data from any usage of Soliris among pediatric patients. PNH is predominantly a condition among adults and very rare among pediatric patients.

REVIEW COMPONENTS:

Background

Soliris (eculizumab) was proposed by the sponsor for "treatment of PNH." The sponsor agreed to modify the indication statement to describe hemolysis as the major treatment effect of Soliris. Indeed, the entire Soliris clinical development program was engineered to establish Soliris treatment effects upon hemolysis and this effect was established with robust clinical evidence.

During the review cycle, the sponsor initially proposed a complex risk management program that was referred to as the [redacted] Consequently, the sponsor revised the risk minimization plan to still require participation of all patients within a safety registry and educational program but this modified program (Soliris Guardian Program) eliminated verification mandates. Instead, compliance with vaccination expectations and other usage requirements will be on a voluntary basis. This proposal is reasonable in light of the consideration that Soliris prescription/administration is expected to be under the aegis of hematologists and other well-trained health care personnel. Additionally, the requirement for intravenous administrations of Soliris every 14 days, provides a strong likelihood that patients will frequently and regularly interact with health care personnel.

Brief Regulatory Timeline

- September 15, 2006 - submission of BLA
- October 30, 2006 Filing meeting, BLA was assigned a priority review
- November 14, 2006 Filing action date
- January 4, 2007 Mid-cycle meeting
- March 16, 2007 PDUFA due date

Clinical Review

The clinical review was performed by Dr. Andrew Dmytrijuk. Dr. Kathy Robie Suh provided Team Leader expertise to the review and a secondary review. I have examined the clinical review and I concur with the findings, comments and recommendations. The review was finalized prior to labeling discussions. Hence, some of the recommendations are not specifically consistent with the final labeling, in terms of textual wording. However, the substance of the recommendations is consistent with the final labeling.

Substantial evidence of safety and effectiveness for Soliris was obtained from the clinical study referred to as the TRIUMPH study (A hemoglobin stabilization and transfusion reduction efficacy and safety clinical investigation, randomized, multi-center, double-blind, placebo-controlled, using eculizumab in paroxysmal nocturnal hemoglobinuria).

Triumph study:

a. Major study features:

Triumph was a randomized, double-blind clinical study that compared Soliris to placebo among 87 transfusion-dependent adults PNH patients. The study's co-primary endpoints were a (superiority) comparison of "hemoglobin stabilization" rates and a comparison of the number of RBC units between the two study groups. Prior to initiation of the active treatment periods, patients were observed over a period of time (up to three months) to establish a hemoglobin "set point" that identified the hemoglobin criterion applicable to establishing "hemoglobin stabilization." The set point identified the lowest hemoglobin value that would necessitate RBC transfusion.

Soliris was administered at the dose recommended within the product label; 600 mg once weekly for four weeks followed by 900 mg on the fifth week and then 900 mg on alternate weeks, thereafter.

The major study evaluations consisted of frequent hematologic evaluations (serum lactic dehydrogenase (LDH), free hemoglobin, blood counts and flow cytometry) as well as clinical, clinical chemistry and certain patient reported outcome (FACIT-fatigue and EORTC QLQ-30) evaluations--all obtained at baseline and throughout a 26 week treatment period.

The study's primary endpoint analytical methodology consisted of a Fisher's comparison of the hemoglobin stabilization rates and the comparison of the total number of RBC units used by each patient within each group used a Wilcoxin rank sum comparison. Secondary endpoints (transfusion avoidance, area-under-the-curve lactate dehydrogenase (LDH), FACIT-fatigue outcomes) were also analyzed using prespecified methods.

b. Major study findings:

Both co-primary endpoints were directly related to evidence of Soliris reduction in hemolysis and both demonstrated statistical persuasiveness ($P < 0.001$). This reduction

Antibody formation to Soliris was detected in three patients (out of 196) and resulted in no apparent clinical consequences.

Statistical Review:

The statistical review was performed by Dr. Richard Chen, lead statistician for the BLA. The findings from her review were secondarily reviewed by Dr. Jyoti Zalkikar, Biometric Team Leader.

I have read Dr. Chen's statistical review report and I concur with his statistical analyses, findings and comments that the sponsor has provided persuasive evidence of Soliris safety and efficacy.

Clinical Pharmacology and Biopharmaceuticals (OCPB) Review

The clinical pharmacology and biopharmaceutical review was performed by Dr. Jang-Ik Lee. The findings from the review were secondarily reviewed by Dr. Hong Zhao, Team Leader. Dr. Rajanikanth Madabushi provided a phaarmacometrics review.

I have read the clinical pharmacology and biopharmaceuticals review report and I concur with the observations and comments.

The OCPB review noted that pharmacodynamics of Soliris are mainly indicated by reductions in serum LDH, a measure that is readily available to clinicians and that may be clinically useful for monitoring Soliris effects. This monitoring is briefing described within the Soliris label. The OCPB reviewers requested no phase 4/PMC studies.

Chemistry and Microbiology

The Chemistry review was performed mainly by Dr. Michelle Jessen. However, other CMC reviewers included Drs. Joseph Kutza, Gurpreet Gill-Sangha and Kurt Brorson. Her report was secondarily reviewed by Dr. Patrick Swann as supervisory chemist.

I have read the summary of the chemistry review findings and concur with the results. Dr. Jessen observed that the supplied chemistry and manufacturing information was sufficient to support the product's approval. She also noted that inspection of all manufacturing facilities revealed satisfactory findings. Multiple CMC PMC were agreed to by the sponsor.

Notably, the sponsor had not supplied an acceptable neutralization assay for the detection of antibody formation. One of the PMC relates to the need for this assay although the Soliris bioactivity appears so intimately related to the reduction of serum LDH, the in-use, patient data may provide the most meaningful measure of neutralizing antibody formation.

Dr. Brenda Uratani provided a microbiology review that recommended approval. I have examined Dr. Uratani's summary findings, including inspectional findings.

Pharamcology/Toxicology

The pharmacology/toxicology review was performed by Dr. Siham Biade and was secondarily reviewed by Dr. Adebayo Laniyonu.

I have read the pharmacology/toxicology recommendations and I concur with the observations. The reviewers noted that the submitted pharmacology/toxicology data support the approval of Soliris and with no need for PMC nonclinical studies.

In general, animal testing used a monoclonal antibody that was bioactive within animals (a surrogate antibody). Soliris was not used since it appeared specific for human proteins and was inactive in the tested animals.

Pediatric Safety and Efficacy

As previously noted, no pediatric data were supplied and the sponsor is to collect any pediatric usage information in the post-marketing period.

Proposed Labeling

During the review cycle, FDA and the sponsor developed multiple revisions of the Soliris product label. These revisions largely related to the description of the clinical studies and the safety information. I have reviewed the final product label and concur with the text.

Office of Drug Safety/Division of Medication Errors and Technical Support (ODS/DMETS/)

Linda Wisniewski, RN (Safety Evaluator) provided a DMETS review of the proposed product label, container label and proprietary name. The secondary review of her findings was performed by Nora Roselle, PharmD. (Team Leader). The team found the proposed labeling of cartons/containers acceptable as was the proprietary name, Soliris.

Division of Scientific Investigation (DSI)

Dr. Tejashri Purohit-Sheth provided a report of the FDA inspectional findings at selected clinical sites involved in the TRIUMPH study. The secondary reviewer on his report was Dr. Leslie Ball. The inspectors found the clinical data reliable. Only minor protocol violations were detected. I have read the report and concur with the findings.

Financial Disclosure

As noted in Dr. Dmytrijuk's review, the sponsor has submitted required financial disclosure information and the information is acceptable.

Consultations

The SEALD (study endpoint and label development) team provided a consult regarding the quality of life measures used in the Soliris clinical development program. The team noted that Soliris studies demonstrated persuasive treatment effects as evidenced by changes in the FACIT-fatigue and EORTC QLQ-C30 scores. The team regarded use of the words, "health-related quality of life" in the label but discouraged the word, "fatigue." During labeling discussions, the sponsor insisted upon the use of "fatigue" and the

SEALD team, at one point, acknowledged the size of the treatment effects in FACIT-fatigue and did not object to the use of the word, "fatigue." The team did object to the

Office of Surveillance and Epidemiology (OSE) consultation (Joyce Weaver, Betsy Scruggs, Jeanine Best and Claudia Karwolski) participated in the review of the risk minimization plan and were instrumental in working with the sponsor to draft an acceptable program. The OSE consultants also participated in final labeling discussions and provided detailed feedback on development of a Medication Guide.

32 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 5, 2007

From: Kathy M. Robie-Suh, M.D., Ph.D. K. Robie-Suh M 3/5/07
Medical Team Leader, Hematology
Division of Medical Imaging and Hematology Drug Products (HFD-160)

Subject: Medical Team Leader Secondary Review
BLA 125166, submitted 9/15/06
Soliris (eculizumab; h5G1.1 G2/G4 mAb) for treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH)

To: BLA 125166

Background:
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired intravascular hemolytic disorder having an incidence of 1 to 2 per million and prevalence of 12 per million. The disorder is due to a somatic mutation in the PIG-A gene which is necessary for the synthesis of GPI-anchors. The mutation leads to a deficiency of the GPI-anchored terminal complement inhibitor CD59 on the surface of clonal populations of hematopoietic stem cells. Normally CD59 blocks formation of the terminal complement complex on the red blood cell (RBC) surface and thereby prevents hemolysis. Though PNH cells are present in all blood cell types, PNH RBCs are more sensitive to complement mediated lysis and characteristics of the disease reflect RBC hemolysis. The clinical manifestation of this disorder is a highly variable anemia that may be accompanied by fatigue, pain and intermittent frank hemoglobinuria. Patients may also have mild thrombocytopenia and granulocytopenia. Patients have an increased frequency of thromboses (predominantly venous) and may develop aplastic anemia or evolve into acute myeloblastic leukemia. Patients have a shortened lifespan. Intravascular hemolysis is monitored most commonly by measuring the release of the enzyme lactate dehydrogenase (LDH) into the plasma. There are no labeled treatments for PNH. Patients usually require RBC transfusions, which increase hemoglobin concentration and may help decrease hemolysis by suppressing hematopoiesis of abnormal RBCs. Corticosteroids have been used to suppress inflammation which may stimulate complement activation. Patients often receive anticoagulants to prevent and treat thrombosis.

Eculizumab is a humanized version of a murine monoclonal antibody that binds to human complement 5 (C5) component protein and results in inhibition of complement-mediated hemolysis. The drug has been developed for use in treating PNH to reduce hemolysis of PNH cells thereby preventing anemia and consequent need for red blood cell transfusions. Eculizumab is not currently approved in the U.S. or anywhere in the world for any use. In this application the sponsor is seeking marketing approval of eculizumab for treatment of PNH in adult patients. The application has been granted priority review.

Findings of the Clinical Review:

Efficacy:

The primary Clinical Review of eculizumab was done by Dr. A. Dmytrijuk (dated 2/1/07, signed 02/28/07). To support the indication the sponsor has conducted a single adequate and well-controlled study evaluating the efficacy and safety of eculizumab in transfusion-dependent PNH patients. This study (C04-001, TRIUMPH) was a randomized, multicenter, double-blind, placebo-controlled investigation of eculizumab involving 109 enrolled patients (88 randomized, 87 randomized and treated) patients with transfusion-dependent PNH. Qualified patients were adult males or females (age ≥18 yrs) having a GPI deficient RBC clone (Type III cells) ≥10% and stable dose of other therapies [e.g., immunosuppressive therapy, corticosteroids, erythrocyte stimulating agent (ESA), iron supplementation). Notable exclusion criteria were mean hemoglobin prior to transfusion of >12.5 g/dL over the prior 12 months, neutrophil count ≤500/mcL, history of meningococcal disease, history of bone marrow transplantation. Following enrollment patients underwent a 13 week observation period. Patients having LDH level ≥1.5 times upper limit of normal, who received at least 1 RBC transfusion during the observation period within 48 hours of experiencing either a hemoglobin of ≤9 g/dL with symptoms or a hemoglobin ≤7 g/dL without symptoms [hemoglobin "set point"][hemoglobin value also must be within 1.5 g/dL of the previously calculated mean hemoglobin pre-transfusion for the previous 12 months], and who had platelet counts ≥100,000/mcl were randomized at the conclusion of the observation period. Important criteria for exclusion were evidence for or suspicion of bacterial infection, history of meningococcal disease or bone marrow transplant, neutrophil count ≤500/mcl, mean hemoglobin prior to transfusion of >10.5 g/dL during preceding year, pregnant or breast-feeding. All patients were vaccinated against *Neisseria meningitidis* at least 14 days prior to beginning treatment. Patients were randomized to eculizumab 600 mg IV (via 25-45 minute infusion) weekly for 4 weeks followed by 900 mg in week 5 and then every 14 days thereafter to a total of 26 weeks of treatment or placebo for 26 weeks. Patients were followed for 12 weeks after their last dose of study drug. Randomization was stratified on packed RBC transfusions (low, mid and high) during the year prior to screening. Efficacy was assessed using the co-primary endpoints of hemoglobin stabilization and RBC transfusion requirement (number of units). For the hemoglobin stabilization endpoint, those patients who dropped out of the study or were transfused above their set points during the treatment phase were categorized as failures. For the number of units of packed red blood cells (PRBCs) transfused, each patient's units of PRBCs transfused after randomization to 26 weeks was calculated. Additional endpoints included lactate

dehydrogenase area-under-the-curve (AUC) during the study, changes in the functional assessment of chronic illness therapy fatigue (FACIT-F) assessment score, quality of life (QOL) assessment using the EORTC-C30 instrument, and thrombosis. Important safety outcomes were occurrence of infections

In Study C04-001, of 88 patients randomized, 87 were treated (43 eculizumab, 44 placebo). Baseline characteristics were reasonably well-balanced between treatment groups in this somewhat small study. Mean age of patients was similar in the two treatment groups (42.1 yrs in eculizumab; 38.4 yrs in placebo group). There were relatively more females in the placebo group than in the eculizumab group (65.9% and 53.5%, respectively) and patients with blood type A+ predominated in the placebo group (25.6% in the eculizumab group; 45.5% in the placebo group) while patients with blood type O+ predominated in the eculizumab group (37.2% in the eculizumab group; 22.7% in the placebo group). About 90% of patients were Caucasian. Mean hemoglobin prior to transfusion was approximately 8.0 g/dL and mean number of RBC units transfused was about 19.5 in both groups. About 63% of patients had symptomatology of severe or worsening fatigue associated with transfusion. Nine patients in the eculizumab group and 8 patients in the placebo group had history of major vascular event. There was concomitant use of antithrombotic agents in 55.8% of patients randomized to placebo and 45.5% of patients randomized to placebo. Ten patients in the placebo group discontinued study treatment prematurely, all due to lack of efficacy; all 10 continued followup to complete study assessments. Two patients in the eculizumab group discontinued prematurely, 1 due to an adverse event (pregnancy) and one due to patient request. Results for the primary efficacy analyses are summarized in the following table.

Primary Efficacy Results for Study C04-001 after 26 Weeks of Treatment

Randomization Strata	N	Eculizumab N=43	Placebo N=44	p-value
Overall:	87			
Hb stabilized		21/43 (48.8)	0/44 (0.0)	<0.00001[a]
Mean units PRBC transfused (SE)		3.0 (0.67)	11.0 (0.83)	<0.00001[b]
4 to 14 units:	30			
Hb stabilized		12/15 (80.0)	0/15 (0.0)	<0.00001[a]
Mean units PRBC transfused		0.4 (0.29)	6.7 (0.72)	<0.00001[b]
15 to 25 units	35			
Hb stabilized		5/17 (29.4)	0/18 (0.0)	<0.00001[a]
Mean units PRBC transfused		4.2 (1.14)	10.8 (1.17)	<0.00066[b]
>25 units	22			
Hb stabilized		4/11 (36.4)	0/11 (0.0)	0.090[a]
Mean units PRBC transfused		4.5 (1.59)	17.0 (1.04)	0.00030[b]

[a] Fisher's exact test; [b] Wilcoxon's rank sum test

No placebo-treated patients achieved hemoglobin stabilization. Overall and within each of the strata, more eculizumab-treated patients than placebo-treated patients achieved hemoglobin stabilization, and the difference between treatment groups was statistically

significant and robust overall. Results within the low and medium transfusion strata (≤25 units PRBC) strongly supported the overall efficacy result. Units of PRBC transfused similarly were significantly less in the eculizumab group than in the placebo group. Efficacy results were similar for males and females.

In addition, overall and within each stratum AUC for LDH was significantly less over the course of the study in the eculizumab group as compared to the placebo group (mean AUC: eculizumab group, 81140; placebo group, 429874). At completion of study treatment (Week 26) for assessed patients a modest between groups difference was seen in FACIT-Fatigue score improvement (53.7% of eculizumab patients as compared to 20.5% of placebo patients improved by at least 4 points). Two eculizumab patients and 5 placebo patients were missing data for this analysis.

Study C04-001 was supported by an additional study, Study C04-002 (SHEPHERD Study), which was an open-label, multicenter study designed primarily as a safety study. The inclusion and exclusion criteria for this study were similar to those for Study C04-001 except that Study C04-002 allowed lower platelet counts (≥30,000/mcl) and required only 1 RBC transfusion in prior 24 months. The study included a 12 week enrollment phase followed by a 2-week screening phase, followed by 52-weeks of treatment and 8 weeks of additional followup. In this single arm study, efficacy was assessed by change in LDH AUC over time. Treatment duration was planned for 52 weeks. The BLA submission contains an interim report of 26 weeks treatment. A total of 97 patients were enrolled and treated. One patient died after 5 doses of study drug due to cerebral herniation and 96 patients completed all visits. Baseline characteristics, including pre-treatment LDH levels were similar to those for patients in Study C04-001. In this study 42/97 patients had a history of thrombosis and and 63.9% of patients were on concomitant antithrombotics during the study. Mean change in LDH from baseline to 26 weeks was a decrease of 325376 U/L×day. Mean LDH level at 26 weeks was 270 (mean at baseline was not calculated). Of the enrolled patients, 55.7% of patients had no transfusions. Percentages of PNH Type III RBC increased from a median of 33.5% at baseline to 50.6% at 26 week visit.

The sponsor attempted to evaluate efficacy of eculizumab for reducing likelihood of thrombosis in patients with PNH. In Study C04-001, 9 patients in the eculizumab group had a history of a total of 12 thrombosis events and 8 patients in the placebo group had a history of 8 thrombosis events. During that study only one patient in the placebo group experienced a thrombotic event (hepatic vein thrombosis) and none in the eculizumab group. The small number of patients in this study and the low thrombotic event rate preclude meaningful comparison of rates between groups in this controlled study. The sponsor seeks to augment the data by performing an analysis across all studies of eculizumab in PMH patients comparing frequency of thrombosis during treatment with eculizumab with their historical rate of thrombosis during the total time before and during the year prior to study entry as documented in the case report form. Events included in this analysis included those classified as major adverse vascular events (MAVE). MAVE

included thrombophlebitis/deep vein thrombosis, pulmonary embolus, cerebrovascular accident amputation, myocardial infarction, transient ischemic attack, unstable angina, renal vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis (Budd-Chiari), gangrene, acute peripheral vascular occlusion, and sudden death. Event rates were calculated by dividing the total events reported (historical) or observed (during study treatment) by the calculated total amount of time all patients in the study had been on eculizumab (patient years). In all the PNH studies in the eculizumab treated patients, the calculated MAVE rates per 100 patient years were less during study treatment than during the time prior to the study. These results using the 12 months prior to eculizumab treatment are shown in the sponsor's table below.

Table 5.4.2-1: Thromboembolic Events in Patients During the 12 Months Prior to Start of Eculizumab Treatment and During Eculizumab Treatment in C04-001, C04-002, C02-001/E02-001/X03-001 and E05-001

	C04-001	C04-002	C02-001/ E02-001/ X03-001	E05-001 (All studies combined)
Pre-Treatment				
Patients (n)	43	97	11	195
MAVE Events (n)	6	23	3	33
Patient Years (n)	42.9	93.8	11.0	191.8
MAVE Event Rate (n per 100 patient years)	13.98	24.51	27.27	17.21
SOLIRIS™ Treatment				
Patients (n)	43	97	11	195
MAVE Events (n)	0	2	0	2
Patient Years (n)	21.8	48.2	35.8	164.1
MAVE Event Rate (n per 100 patient years)	0.00	4.15	0.00	1.22[1]

[1]P=0.013 Eculizumab vs. Pre-Treatment

In the controlled clinical study (Study C04-001), MAVE rate prior to study treatment were lower in the patients randomized to placebo (2.34 per 100 patient years) than in those randomized to eculizumab (5.18 per 100 patient years). The MAVE rate in placebo-treated patients during the study was 4.38 per 100 patient years. Average years per patient prior to treatment were 10.7 and 7.2 in the placebo and eculizumab treatment groups, respectively.

During these studies approximately 54% of patients had received antithrombotic agents prior to start of eculizumab. These medications were allowed as concomitant treatment in the studies and about half of patients were on anticoagulation during the study. The apparent diminution in MAVE rate with eculizumab was confined to patients who had been on anticoagulants prior to study. (Actually, MAVE rates rose in the STUDY C04-002 study during eculizumab treatment in patients who had not been on anticoagulants prior to the study). Because anticoagulant use was common and was not controlled or carefully documented in terms of dose, dose adjustment, starting and stopping, monitoring and so forth, and because there was not a concurrent control for this analysis it is not possible to distinguish between an effect of anticoagulation management and a

possible effect of eculizumab. Also, there was no prospective plan for verifying or validating the quality of the data collection on event rates prior to study enrollment. Thus, the sponsor's analysis must be considered exploratory. In addition to there being a lack of evidence to support efficacy on the thrombosis endpoint, there is concern that highlighting the low thrombosis rates generally seen in these PNH studies may mislead patients or health care providers into thinking anticoagulation can be discontinued in high risk patients who are receiving eculizumab.

Safety:
The safety information is the application is reviewed, summarized and discussed in detail in the Medical Officer's review by Dr. A. Dmytrijuk (dated 2/1/07, signed 2/28/07). The major findings will be summarized here.

In the controlled study in PNH patients (Study C04-001), 43 patients were exposed to eculizumab. Two patients in the eculizumab group discontinued prematurely, 1 due to an adverse event (pregnancy) and one due to patient choice. In the placebo group, 10 patients discontinued, all due to lack of efficacy. One patient in the placebo group experienced a portal vein thrombosis during the study; no patients in the eculizumab group experienced thrombosis in this study. Adverse events that were notably more common in the eculizumab treated patients than in the placebo treated patients were: headache (44.2% and 27.3%, respectively), back pain (18.6% and 9.1%, respectively), fatigue (11.6% and 2.3%, respectively), and respiratory tract infection (7.0% and 2.3%, respectively). Viral infection (2.3% and 11.4%, respectively), urinary tract infection (2.3% and 9.1%, respectively) and paroxysmal nocturnal hemoglobinuria (2.3% and 6.8%, respectively) were more frequent in the placebo group than in the eculizumab group. There were no deaths in this study.

Among 193 PNH patients who received eculizumab in uncontrolled studies serious adverse events occurring in 2 or more patients were: viral infection (2.6%), anemia (1.6%), pyrexia (1.6%), hemolysis (1.0%), and headache 2.1%). Serious adverse events occurring in more that 1 patient among the 140 patients who received eculizumab in Studies C04-001 and C04-002 included: anemia (2.1%), hemolysis (1.4%), intervertebral disc protrusion (1.4%) and pyrexia (1.4%) and headache (1.4%).

Across all PNH studies overall infections did not seem to be more frequent in patients who received eculizumab than in those who received placebo. The incidence of herpes simplex infection appeared to be increased in PNH patients treated with eculizumab (8/140; 5.7%) as compared to none in placebo patients.

Because eculizumab inhibits complement activation, it may impair neutrophil and monocyte function and impair the ability of the patient to clear infections with encapsulated orgainisms. For this reason all patients were required to be vaccinated against *Neisseria meningitides* at least 2 weeks prior to starting study treatment. There have been 3 cases of Neisseria meningitis in patients receiving eculizumab. These were:

a 22 year old unvaccinated woman with idiopathic membranous glomerulonephritis who had received eculizumab for about 7 months; a 54 year old vaccinated female PNH who had been on eculizumab for approximately 14 months; and a 24 year old male vaccinated PNH patient who had received exulizumab for approximately 12 months. No patients died but the unvaccinated patient had a complicated course with amputation of parts of some digits due to gangrene, pulmonary embolus, and pneumonia and she was discharged to a rehabilitation facility after prolonged antibiotic treatment.

In the PNH studies patients were tested for human antihuman antibodies (HAHA) after eculizumab treatment and 2 patients were found to have IgG titers of 1:20 and one patient had an IgM titer of 1:20 and 1:100. No patients developed a rebound in hemolysis with these antibodies. Also, because of concern of rebound hemolysis after discontinuing eculizumab it was planned to follow patients after discontinuation of eculizumab, but few patients in the controlled study discontinued eculizumab prematurely and most patients continued into extension studies of eculizumab after completing study treatment.

In the eculizumab database of PNH patients, a total of 4 patients have died. These were: a 31 year old man with PNH and hemosiderosis in C04-002 who experienced low back pain was hospitalized and suffered a pulmonary embolus 31 days after last eculizumab, had a hemorrhagic cerebral infarction and cerebral herniation and died; a woman [redacted] patient in a physician-sponsored study who experienced exacerbations of cholecystitis and fever about 2 months after last eculizumab dose, abdominal pain and presumed sepsis died due to a CVA; a man in E05-001 who had PNH and myelodysplastic syndrome (MDS) developed cellulitis, sepsis and acute renal failure after [redacted] was hospitalized, developed a viral infection and died due to worsening of his MDS; a woman who died after 13 months on eculizumab of metastatic adenocarcinoma. There is also some experience with eculizumab in other indications, including rheumatoid arthritis, bullous pemphigoid, systemic lupus erythromatosis, idiopathic membranous glomerulonephropathy, psoriasis and dermatomyositis (984 total patients; about 666 exposed to eculizumab). Duration of exposure in these studies generally was longer than in the PNH studies. There have been 3 deaths of patients in these studies: a woman who received placebo in C01-004, a study in rheumatoid arthritis, who experienced acute respiratory distress post-surgery for an incarcerated hernia and died presumably of a pulmonary embolus; a 60 year old woman with rheumatoid arthritis who received eculizumab in Study E99-01, who developed bacterial sepsis followed by Candida sepsis after cholecystectomy and died after 8 months of eculizumab therapy; a man in CC99-004 with idiopathic membranous glomerulonephropathy who died [redacted]

Special Populations:
Pediatrics: No pediatric patients have received eculizumab. PNH is an uncommon disease occurring in only about 1-2 per million persons. The sponsor was granted Orphan Drug status for the drug for the PNH indication on 8/20/03; consequently

pediatric studies are not required under PREA. The sponsor has requested an exemption from any requirement to assess eculizumab in the pediatric PNH subpopulation. Clinical review recommends that this request be granted. Any pediatric patients treated may be followed in a post-marketing registry.

Pregnancy and Lactation: The Pediatric and Maternal Health Staff (PMHS) has provided comment on the proposed labeling for eculizumab. (See Memorandum from Dr. K. Feibus, dated 2/22/07, signed 2/28/07). The PMHS team comments and recommendations for the package insert included that: the Labor and Delivery section of the label be deleted, since there is no information; human IgG crosses the placenta and, therefore, eculizumab also is expected to cross the placenta; eculizumab will likely be Pregnancy Category C and sclass should be used during pregnancy or in women not using adequate contraception unless the potential benefit justifies the potential risk to the fetus; IgG is excreted in human milk, therefore eculizumab is expected to appear in the breast milk.

The PMHS review recommended that in the registry the sponsor plans to establish for patients with PNH who use eculizumab, the registry should be used to prospectively follow pregnancies with eculizumab exposure and their maternal and neonatal outcomes.

Other Information:
Chemistry: 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 IgG_2 sequences in constant region 1, the hinge, and the adjacent protion of constant region 2, and human IgG_4 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. The protein molecule has an expected molecular mass of 148,523 Daltons.

The chemistry, manufacturing, and controls (CMC) (Product) information for eculizumab drug substance has been reviewed by B. Urtani, Ph.D. (review signed 2/23/07). The review found the drug substance section of the application acceptable fro a microbiology product quality perspective. Lonza Biologics, NH, the drug substance manufacturer, and Alexion Pharmaceuticals, CT, for release testing, were found to be in acceptable GMP compliance.

The review of the drug substance control of source and Starting Materials of Biological Origin, Generation of Cell Substrate, Cell banking system, characterization, batch analyses, justification of specifications, reference standards, and stability sections of the application were reviewed by Office of Biotechnology Products, Division of Monoclonal Antibodies (OBP/DMA) (review by M. Frazier-Jessen, Ph.D. et al., final signature 2/27/07). Manufacturing information was found acceptable to support product approval. A number of PMCs were recommended to provide additional information to assure the

continued safety of the product. The review states that these have been agreed to by the sponsor and are as follows:

1. Alexion commits to developing 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.

2. Alexion commits to developing 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.

3. Alexion commits to revalidating the linearity and accuracy of the Osmolality method across the full specification range using a combination of product samples diluted to lower osmolality and product samples spiked with osmolality standards. The revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

4. Alexion commits to revalidating the linearity of the IEF method across a load range of [redacted] The revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

5. Alexion commits to revising the IEF method SOP to specify that the method is validated only for a [redacted]. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

6. Alexion commits to improving and revalidating the existing hemolytic assay. Improvements include increasing the number of sample replicates and qualifying the chicken erythrocytes reagent. The revised method SOP and revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

7. Alexion commits to developing a new quantitative biological activity assay to replace the existing hemolytic assay, or submit documentation to FDA demonstrating with due diligence that a suitable assay could not be feasibly developed. This information will be submitted to the BLA as a CBE 30 by February 29, 2008. Validation of the quantitative biological activity assay will be submitted by July 9, 2008.

8. Alexion commits to providing FDA with a completed drug substance and drug product container closure system leachables evaluation using end-of-shelf-life, long-term 2 – 8°C stability samples. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

9. Alexion commits to develop a suitable [redacted] assay and subsequently confirm [redacted] on three drug substance batches. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

Pharmacology: The pharmacology and toxicology data have been reviewed in detail by S. Biade, Ph.D. (review signed 2/23/07). Notable review findings are summarized briefly here.

Early non-clinical investigations showed that eculizumab did not cross-react with C5 complement of non-primate and non-human primate species. Activity against human C5 was established by measuring the ability of eculizumab to block C5b-9 dependent lysis of pre-sensitized chicken erythrocytes by human serum *in vitro*. Because the molecule shows species specificity with regard to complement inhibition (inhibits only human C5 complement), all non-clinical studies safety studies (safety pharmacology, general toxicity, and reproduction toxicology studies) were done with a murine anti-mouse C5 whole antibody (BB5.1) ("surrogate mAb"). Also, there are no murine models of PNH, so the sponsor studied the murine anti-mouse C5 antibody in mouse models of arthritis, lupus-like autoimmune disease, and asthma which potentially involve C5 and evidence of complement inhibition activity was seen in these models.

No genotoxicity studies have been done (in accordance with ICH S6 Guidance) and no carcinogenicity studies have been done, because of lack of cross-reactivity with C5 in the species usually used for these tests. No placental transfer studies have been done with eculizumab or the similar mouse antibody. However, IgG antibodies are known to cross the placental/fetal barrier through an FcRn receptor mediated mechanism, so eculizumab is felt to have the potential for transfer across the placenta.

The Pharmacology/Toxicology Review describes that, "In a 4 week, repeat dose toxicity study, no toxic signs, based on mortality, clinical observations and body weights, were observed in mice treated for 4 weeks with 30, 60, or 90 mg/kg/week (2-4, 4-8, and 6-12 times the human dose) by bolus injection. Similar hemolytic inhibition was obtained at 60 and 90 mg/kg/week. Therefore, 60 mg/kg/week was selected as the maximum dose

for subsequent studies." In a 26 week study in mice where 60 mg/kg/week was the high dose, there were some clinical signs and microscopic findings and some unexpected deaths in control and high-dose, but not low dose, animals. The Pharmacology/Toxicology Review comments that, "Because of the higher incidence in clinical signs and histopathological findings (lungs, ears, eyes) in the low and high dose treatment groups compared to the control animals, an NOAEL could not be established in this study." Toxicokinetics and antibody measurement were not conducted in any of the toxicology studies. Hemolytic activity was measured as an indicator of systemic exposure.

Reproductive and developmental toxicity studies done in mice established a NOEL for female toxicity, for male and female fertility, reproductive performance and fetal effects of $\geq$60 mg/kg/week when BB5.1 was administered prior to mating and through early gestation. For male toxicity the NOAEL was 30 mg/kg/week. When BB5.1 was administered to pregnant mice through organogenesis, the NOAEL for maternal toxicity and reproductive performance was 60 mg/kg/week and the NOAEL for embryo-fetal development toxicity was 30 mg/kg/week. In the mouse reproduction studies there were three malformations (2 unilateral retinal dysplasias and 1 umbilical hernia) among 230 offspring of high-dose (60 mg/kg/week) animals. In studies where BB5.1 was administered from implantation through weaning in mice, a NOAEL of $\geq$60 mg/kg/week was established for F_1 pup development and reproductive performance.

The Pharmacology/Toxicology Review found no unresolved toxicology issues and recommended that from the perspective of nonclinical pharmacology and toxicology, Soliris may be approved. There were no recommendations for postmarketing studies. Recommendations for labeling included Pregnancy Category C classification for eculizumab, comment that it is expected that Soliris will be excreted in human milk, and mention of lack of long-term animal studies for carcinogenic and genotoxic potential of the drug. The exact wording of these recommendations from the Pharmacology/Toxicology Review is as follows:

Pregnancy (Category C)

8.1 Pregnancy

Pregnancy Category C:

Soliris is a recombinant IgG molecule (humanized murine anti-C5 antibody), and IgG molecules are known to cross the placenta. Developmental abnormalities and an increased rate of dead and moribund offspring were observed in animal studies (mice) that used a surrogate murine anti-C5 antibody at 2 – 8 times the human dose of Soliris. There are no adequate and well-controlled studies in pregnant women. 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-C 5 antibody that approximated 2-4 times (low dose) and 4-8 times (high dose) the recommended human Soliris dose. 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, [redacted] antibody-treated mothers also had a higher number of male offspring that became moribund or died (1/25 controls, 2/25 low dose group, 5/25 high dose group) [redacted] Surviving offspring had normal development and reproductive performance.

[redacted]

8.3 Nursing Mothers

It is not known whether Soliris is secreted 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 breast milk antibodies 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 breastfeeding.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been conducted to evaluate the carcinogenic and genotoxic potential of Soliris. Effects of Soliris 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.

Clinical Pharmacology: Clinical Pharmacology and Biopharmaceutics review was conducted by J.-I. Lee, Pharm.D., Ph.D. (signed 2/28/07). The review found the application acceptable for approval and did not recommend any post-marketing commitments from clinical pharmacology perspective.

Dr. Lee's summary of the clinical pharmacology findings are shown below:
Exposure-Response Relationships

- When determined using a hemolytic assay following a single dose of eculizumab 8.0 mg/kg to patients with rheumatoid arthritis (RA), the onset of complete hemolytic inhibition occurred before the first sampling time (15 min). The duration of the inhibition ranged from 7 to 14 days. The recovery time ranged from 11 to 21 days.
- Based on the pharmacokinetic (PK) / pharmacodynamic (PD) modeling using data collected from patients with idiopathic membraneous glomerulopathy (IMG), RA, and PNH, the total serum (free and bound) concentrations of eculizumab required to block terminal C5 complement activation was roughly 43 mcg/mL.
- Treatment with eculizumab at the proposed dose and dosing regimen resulted in an immediate (from 2109 U/L to 65 U/L by Week 1) and sustained (325 U/L by Week 26) decrease in serum lactate dehydrogenase (LDH) levels as determined in 40 PNH patients (Study C04-001).

Basic Pharmacokinetics

- When studied in patients with RA and systemic lupus erythematosus (SLE) following a single dose, a striking feature of eculizumab concentration-time curve is the presence of second peak at approximately 2 days post dose.
- Eculizumab PK have not been assessed following a single dose to PNH patients.
- Based on a population PK modeling with sparse sampling in a multiple dose study, the clearance of eculizumab for a typical PNH patient weighing 70 kg was 22 mL/hr and the volume of distribution was 7.7 L. The estimated half-life was 272 ± 82 hrs (mean ± SD).

- The mean observed peak and trough serum concentrations of eculizumab by week 26 following the administration of the proposed dose and dosing regimen were 194 ± 76 mcg/mL and 97 ± 60 mcg/mL, respectively.

Immunogenicity

- Using a partially validated enzyme-liked immunosorbent assay (ELISA) method, 1 out of 43 (2.3%) PNH patients treated with eculizumab and 1 out of 44 PNH patients treated with placebo demonstrated a detectable level of human anti-human antibodies (HAHA) at the last study visit (Week 26).
- There appears to be no apparent impact of HAHA induction on the efficacy, safety, and PK of eculizumab. However, a definitive conclusion cannot be made based on the small number of PNH patients with positive HAHA response.

Pharmacometrics review (R. Madabushi, Ph.D. (signed 2/28/07) evaluated the sponsor's pharmacokinetic data. The data were based on population PK modeling using sparse sampling. The review found the following:

1) Based on the population pharmacokinetic modeling, the clearance of eculizumab for a typical PNH patient weighing 70 kg was 0.022 L/hr and the volume of distribution was 7.7 L. The half-life was 272 ± 82 hrs (mean ± SD).
2) The mean observed peak and trough serum concentrations of eculizumab by week 26 were 194 ± 76 µg/mL and 97 ± 60 mcg/mL respectively.
3) Based on the PK/PD modeling, the total serum (free and bound) concentration of eculizumab required to block 50% of terminal complement activation is roughly 43 µg/mL (EC_{50}).
4) Treatment with Eculizumab with the proposed dosing regimen results in immediate (from 2109 ± 965 U/L to 652 ± 278 U/L by week 1) and sustained (326 ± 438 U/L by week 26) lowering of LDH levels.

The review concluded, "Treatment with Eculizumab with the proposed dosing regimen result in immediate and sustained decrease in intravascular hemolysis as evidence by lowering of LDH levels."

Office of Safety and Epidemiology/ Division of Surveillance, Research, and Communication Support (OSE/DSRCS) Review of Patient Labeling: The sponsor proposed a Patient Package Insert (PPI) and a Patient Safety Card for distribution with Soliris (eculizumab). This material was reviewed by OSE/DSRCS (J. Best, review dated and signed 2/28/07). DSRCS recommended that the PPI be modified and issued as a Medication Guide, since a Medication Guide is required to be distributed with the product while distributionof a PPI is voluntary. This should enhance the education of patients who receive eculizumab about the drug. DSRCS also recommended that these two pieces (the Medication Guide and the Patient Safety Card) be the only materials used for patient education, so as not to overwhelm the patient. Finally, the Medication Guide should also be included as part of the text of the package insert following the Patient Counseling Information.

Trade Name Review: Review of the proposed trade name, Soliris, by the Division of Medication Errors and Technical Support (DMETS) (L. Wisniewski, 12/20/06) found that while the name was acceptable for existing approved products, there was potential "for strong orthographic and pnonetic similarities" with two other products that are currently under review, [redacted] and only the first of these three to be approved should receive the requested name. As of 2/28/07 neither [redacted] has been approved.

Discussion:
The sponsor has provided convincing evidence from a single adequate and well controlled clinical trial (C04-001) of eculizumab versus placebo in PNH patients of efficacy in stabilizing hemoglobin levels and reducing the need for transfusions at the eculizumab dose tested. Hemolysis in these PNH patients is lessened as demonstrated by a rapid and sustained decrease in plasma LDH levels in patients receiving eculizumab. Event rates for thrombosis were too small to allow meaningful statistical comparison between treatment groups. Based on the efficacy analyses in C04-001 the clinical review (Dr. A. Dmytrijuk, dated 2/1/07, signed 2/28/07) concluded,

> Therefore it appears that Eculizumab is effective in stabilizing hemoglobin and decreasing the number of packed red blood cell transfusions required in transfusion dependent PNH patients. Secondary endpoint analyses for transfusion avoidance and LDH AUC provide additional support that Eculizumab is effective in the treatment of PNH. However, QOL measures using the FACIT- F tool and EORTC QLQ-C30 tool are confounded by the fact that no assessment of effect of transfusion on QOL was performed. Furthermore, with regard to the FACIT-F tool it is not clear if the tool measures all of the components of fatigue because fatigue is a multidimensional concept that encompasses both mental and physical attributes. With regard to the EORTC QLQ-C30 tool there is no evidence available to support the validity of the instrument to measure the individual domain or individual symptom constructs. Analyses of the effect of Eculizumab on the incidence of thrombosis are confounded by the fact that approximately 50% of patients in the Eculizumab treatment arm were on concomitant anticoagulant therapy.

The review concluded that conclusions regarding effect of eculizumab on thrombosis were confounded because a majority of patients in Study C04-002 were on concomitant anticoagulant therapy in the study. The application also was consulted to the Study Endpoints and Label Development (SEALD) team for comment on the quality of life assessments and data. The medical review reports that the SEALD team identified concerns, including that it is unclear if the FACIT-F tool measures all components of fatigue and no evidence is available to support the validity of the EORTC QLQ-C30 QOL instrument to measure the individual domain or individual symptom constructs.

Based on the safety database provided, with regard to safety the Clinical Review concluded:

Therefore, Eculizumab appears to be generally safe for the treatment of patients with PNH. However, because of the mechanism of action of Eculizumab on the immune system patients with PNH who are treated with Eculizumab are at increased risk for infections with encapsulated organisms. The sponsor proposes an early alert program and a registry program in order to minimize the risk of infections in patients with PNH were treated with Eculizumab. In addition patients who are to be treated with Eculizumab must be vaccinated with *Neisseria meningitidis* vaccine at least two weeks prior to treatment with Eculizumab as was described in the protocols in the PNH studies.

The Clinical Review recommended that eculizumab be approved for treatment of PNH [redacted] dosing as used in the C04-001 Study.

Conclusions and Recommendations:
Soliris (eculizumab) is being recommended for approval for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) to [redacted] hemolysis [redacted] Soliris is administered intravenously over [redacted] minutes at a dose of 600 mg every 7 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 days later, then 900 mg every 14 days thereafter.

To support the BLA application the sponsor has provided a single adequate and well-controlled clinical trial of eculizumab compared to placebo for 24 week treatment in transfusion-dependent PNH patients and a single-arm, uncontrolled study following PNH patients on eculizumab treatment over 26 weeks. Results of the controlled study clearly demonstrated greater improvement in the co-primary endpoints of number of transfused RBC units required and hemoglobin stabilization and in proportions of patients requiring blood transfusions, and decreases in serum lactate dehydrogenase levels in the eculizumab treated patients as compared to the placebo-treated patients. The Statistical Review (Y. W. Chen, Ph.D., 1/31/07) concluded, "Efficacy results for both two co-primary efficacy endpoints demonstrated the statistical significance favoring eculizumab, overall and by subgroup of historical transfusion stratification." Measures of some quality of life parameters, such as fatigue, also appeared to improve in the eculizumab treated patients as compared to in the placebo patients. However, the quality of life assessments were carried out only prior to transfusion in the control group, so it is not clear whether improvement in fatigue was due to a direct eculizumab effect or, more likely, due to improvement in the hemolysis.

Important aspects for the labeling include:

- There should be prominent inclusion of the necessity of well-documented, up to date immunization of patients against *Neisseria meningitidis* prior to treatment with eculizumab. Patients must be maintained with current vaccinations throughout treatment with eculizumab. Information about Neisseria meningitis risk should be contained in a black box warning, as the sponsor has proposed.

- The label should indicate that active meningococcal infection and/or lack of up to date meningococcal immunization are contraindications for eculizumab use.

- The indications statement should reflect that eculizumab decreased hemolysis in PNH patients. Clinical studies in PNH patients were done in transfusion dependent patients and eculizumab stabilized hemoglobin and reduced the need for red blood cell transfusions in these patients.

- The recommended dosing should be that used in the controlled clinical trial.

- An effect of eculizumab in reducing thromboses in PNH patients has not been shown in the submitted studies. Over half of the patients enrolled in the PNH studies had concomitant use of antithrombotics during eculizumab treatment.

- The patient education materials should be revised to include a Medication Guide and a Patient Safety Card, as recommended by DSRCS.

Though a restricted distribution risk minimization plan is not being recommended for this product, the labeling should prominently reflect the particular risk of meningococcal infections and a patient Medication Guide and Patient Safety Card should be developed for the product as planned by the sponsor and distributed to all patients who receive the drug, as recommended by the DSRCS.

Exact wording of the labeling is being negotiated with the sponsor.

Though the information provided is adequate from a clinical viewpoint to support approval of eculizumab for marketing, additional information is needed to provide more complete information in the labeling to enhance the safe use of the product. Accordingly, the clinical review (Dr. A. Dmytrijuk, 2/28/07) recommends the following clinical post-marketing commitments (PMCs):

The sponsor should be required to do the following:

- Commit to evaluating long-term safety of Eculizumab by analyzing outcomes in the paroxysmal nocturnal hemoglobinuria (PNH) registry program for a time period of no less than five years. At the end of the five year period, a study report will be submitted to the Biological License Application (BLA) that describes the major safety findings from the registry program, including the specific items listed below and proposing labeling changes as appropriate. Additionally, annual interim reports will be submitted to the BLA, along with expedited reports as specified below. All patients within the registry will be followed for the occurrence of:

    - Serious infections, defined as infections necessitating or prolonging hospitalization or resulting in death. The sponsor should commit to collecting follow-up information from these patients to assess the nature of the serious infection, the duration of hospitalization, 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;

    - Use of Eculizumab among pediatric patients under 16 years of age, to include collection of Eculizumab dosage information, as well as the same information being required for adult patients in the registry.

    - Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among babies born to the women exposed to Eculizumab during the pregnancy.

For all the patients being followed in the registry, eculizumab exposure (dose and treatment duration), as well as clinical outcomes and adverse events should be collected. Patients who discontinue eculizumab should be followed for evidence of rebound hemolysis.

Additional PMCs as recommended by the Division of Monoclonal Antibodies, Division of Monoclonal Antibodies, OBP, and detailed under "Other Information: Chemistry" above should also be required.

CLINICAL REVIEW

Application Type	BLA
Submission Number	125166
Submission Code	000
Letter Date	September 15, 2006
Stamp Date	September 15, 2006
PDUFA Goal Date	March 16, 2007
Reviewer Name	Andrew Dmytrijuk, MD
Review Completion Date	February 1, 2007
Established Name	Eculizumab (h5G1.1-mAb)
(Proposed) Trade Name	Soliris
Therapeutic Class	Monoclonal Antibody
Applicant	Alexion Pharmaceuticals, Inc. 352 Knotter Dr. Cheshire, CT 06410
Priority Designation	S
Formulation	Humanized Monoclonal Antibody
Dosing Regimen	600mg via 25-45 minute intravenous infusion every 7+/- 2 days for the first 4 weeks followed by 900mg via 25-45 minute intravenous infusion for the fifth dose 7 +/- 2 days later then 900mg via 25-45 minute intravenous infusion every 14 +/- 2 days thereafter.
Indication	Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria
Intended Population	Patients with Paroxysmal Nocturnal Hemoglobinuria

2/28/07

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LIST OF ABBREVIATIONS:

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
CFR	Code of Federal Regulations
CRF	case report form
DSMB	data safety monitoring board
ECG	electrocardiogram
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30, Version 3.0
FACIT-Fatigue scale	Functional Assessment of Chronic Illness Therapy-Fatigue scale, version 4
GPI	glycosylphosphatidylinositol
HAHA	human antihuman antibody (anti-h5G1.1-mAb)
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IVRS	interactive voice response system
LDH	lactate dehydrogenase
MAVE	major adverse vascular event
MID	minimally important difference
NO	nitric oxide
PD	pharmacodynamics
PK	pharmacokinetics
PNH	paroxysmal nocturnal hemoglobinuria
PRBC	packed red blood cell
QoL	quality of life
RBC	red blood cell

SAE	serious adverse event
SD	standard deviation
TEAE(s)	treatment-emergent adverse event(s)
WBC	white blood cell

EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Eculizumab should be approved for the following indication:

- Treatment of paroxysmal nocturnal hemoglobinuria (PNH) [redacted] The dose proposed is as follows:
    - In the induction phase, 600 mg of Eculizumab is administered every week for the first four weeks and 900 mg of Eculizumab is administered in week five. The maintenance phase consists of a 900 mg dose of Eculizumab every 14 +/- 2 days thereafter. The drug is administered as a [redacted] minute intravenous (IV) infusion.

The rationale for this approval recommendation is based on the following information:

- The efficacy of the proposed therapy is supported by the TRIUMPH (C 04-001) study. This study was a randomized, double-blind, placebo-controlled, multicenter, multinational trial conducted in transfusion dependent patients with PNH. The study showed a benefit of Eculizumab in stabilizing hemoglobin levels and reducing requirement for red blood cell transfusions.
- In addition, the efficacy of Eculizumab for the treatment of patients with transfusion dependent PNH was supported by the SHEPHERD (C 04-002) study. This 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 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.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The sponsor should undertake the usual postmarketing monitoring and reporting. In addition the sponsor proposes a risk minimization program which involves a registry of all PNH patients who are exposed to Eculizumab. In addition to the registry the sponsor proposes to incorporate an early alert program to minimize the risk of infectious adverse events in patients with PNH who are treated with Eculizumab.

1.2.2 Required Phase 4 Commitments

The sponsor should address all of the postmarketing commitments (PMCs) which include both clinical and chemistry/manufacturing postmarketing commitments and are listed as follows:

- Commit to evaluating long-term safety of Eculizumab by analyzing outcomes in the paroxysmal nocturnal hemoglobinuria (PNH) registry program for a time period of no less than five years. At the end of the five year period, a study report will be submitted to the Biological License Application (BLA) that describes the major safety findings from the registry program, including the specific items listed below and proposing labeling changes as appropriate. Additionally, annual interim reports will be submitted to the BLA, along with expedited reports as specified below. All patients within the registry will be followed for the occurrence of:

    - Serious infections, defined as infections necessitating or prolonging hospitalization or resulting in death. The sponsor should commit to collecting follow-up information from these patients to assess the nature of the serious infection, the duration of hospitalization, 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;

    - Use of Eculizumab among pediatric patients under 16 years of age, to include collection of Eculizumab dosage information, as well as the same information being required for adult patients in the registry.

    - Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among babies born to the women exposed to Eculizumab during the pregnancy.

- In addition there are a number of chemistry, manufacturing and controls (CMC) postmarketing commitments which require that the sponsor evaluate human antihuman antibody formation (HAHA) as well as other manufacturing issues. (See CMC review for a list of these PMCs).

1.2.3 Other Phase 4 Requests

None requested.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Eculizumab is a humanized monoclonal antibody that binds to the human C5 complement protein. This results in the inhibition of the terminal complement cascade. CD 59 blocks the terminal complement cascade on normal red blood cells. Red blood cells lacking CD59 are type III red blood cell clones. Patients with paroxysmal nocturnal hemoglobinuria (PNH) lack CD59. The lack of CD59 on the red blood cells of patients with PNH allows the terminal complement cascade to hemolyze these red blood cells. Currently there are no pharmacologically related products other than other monoclonal antibodies used in various other diseases. These monoclonal antibodies share the common adverse event of infusion reaction usually displayed as a hypersensitivity reaction either systemically or locally at the point of infusion. Also because this is a monoclonal antibody with human constant regions HAHA to Eculizumab may develop.

PNH is an uncommon, life-threatening hemolytic anemia. The reported incidence is 1-2 per million. The disease is characterized by chronic intravascular hemolysis. There is release of hemoglobin into the plasma from hemolyzed red blood cells. The hemolysis leads to anemia, thrombosis and fatigue - which are the most common morbidities for this disease. Clinically, the degree of the hemolysis is monitored by levels of serum lactate dehydrogenase (LDH). Currently there are no approved treatments for PNH.

Eculizumab administered in a 30 minute IV infusion at doses > 4 mg/kg or at fixed doses > 600 mg reaches peak serum concentrations in excess of 100 mcg/ml within one hour of infusion. At these doses of Eculizumab terminal complement inhibition is evidenced by the essentially complete inhibition of complement mediated hemolysis. The sponsor notes that the hemolysis in pharmacodynamic assays is inhibited by Eculizumab concentrations in excess of 35 mcg/ml. Concentrations below this threshold result in inadequate inhibition of C5. Hemolysis takes place at concentrations < 20 mcg/ml as measured by the pharmacodynamic hemolytic assay. The sponsor states that the proposed dosing regimen effectively maintains the concentration of Eculizumab at approximately 35 mcg/ml.

The study C04-001, also known as the TRIUMPH study (A Hemoglobin Stabilization in Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab and Paroxysmal Nocturnal Hemoglobinuria Patients), is the pivotal study supporting Eculizumab's safety and efficacy for the treatment of PNH. In addition, information from the open label study C04-002, also known as the SHEPHERD study (Safety in Hemolytic Paroxysmal Nocturnal Hemoglobinuria Patients Treated with Eculizumab: the Multicenter, Open Label, Research Design Study), was submitted by the sponsor to support the safety and also the efficacy of Eculizumab therapy in PNH patients. An additional analysis of the safety of Eculizumab in PNH patients was undertaken using the combined safety database consisting of all of the PNH patients exposed to Eculizumab thus far in the clinical development program. The sponsor, in the submission, lists 196 PNH patients as having been exposed to Eculizumab. The sponsor reported in a teleconference with the division in January of 2007 that one additional patient in a physician sponsored IND was exposed to

Eculizumab that was not reported as part of the safety database for Eculizumab in the BLA submission. The non-PNH studies were reviewed to further analyze the safety database of Eculizumab.

In the 87 patient, double blind, placebo controlled, TRIUMPH study conducted in patients with PNH, the efficacy co-primary endpoints for this study were hemoglobin stabilization and the number of packed red blood cell units transfused during the treatment phase of the study through 26 weeks. The secondary objectives of this study were transfusion avoidance, hemolysis as measured by lactate dehydrogenase (LDH) area under the curve (AUC) during the treatment phase from baseline through 26 weeks. This study also had the exploratory endpoints of LDH change from baseline through 26 weeks, EORTC QLQ-C30 quality-of-life (QOL) changes from baseline through 26 weeks, thrombosis, platelet activity, nitric oxide and free hemoglobin measures from randomization and through 26 weeks.

The 97 patient SHEPHERD study was an open label, multicenter study of Eculizumab administered IV to patients with PNH for 52 weeks. The primary objective of this study was to evaluate the safety of Eculizumab in patients with transfusion dependent PNH. The secondary objectives of this study were to analyze hemolysis reduction as measured by LDH AUC and changes in the functional assessment of chronic illness therapy fatigue (FACIT-F QOL) scale. Exploratory endpoints for this study included health-related QOL as measured by the EORTC QLQ-C30 and measures of thrombosis, platelet activity, nitric oxide and free hemoglobin.

The safety of Eculizumab was supported by information from the TRIUMPH study and an analysis of the safety in all PNH patients exposed to Eculizumab.

1.3.2 Efficacy

In the TRIUMPH study, in the Eculizumab treated group there were 21/43 patients who had hemoglobin stabilization compared to 0/44 patients with hemoglobin stabilization in the placebo group in the TRIUMPH study ($P<<0.0001$). The hemoglobin set point for each patient was defined as ≤ 9 g/dl in patients with symptoms and was ≤ 7 g/dl in patients without symptoms. To achieve a designation of hemoglobin stabilization, a patient had to maintain a hemoglobin concentration above the hemoglobin set point and avoid any red blood cell transfusion for the entire 26 week treatment period. In the Eculizumab group 22/43 patients did not achieve hemoglobin stabilization. When patients were stratified according to transfusion requirements prior to study entry, (low, intermediate and high strata) there was a statistically significant number of patients who achieve hemoglobin stabilization treated with Eculizumab compared to placebo treated patients. The table below shows the results of the primary endpoint of hemoglobin stabilization in the intention to treat population.

Table 10. Hemoglobin Stabilization (ITT)

Randomization strata	Hemoglobin stabilization?	Eculizumab N = 43 n/N (%)	Placebo N = 44 n/N (%)	*P* Value[a]
Overall (N=87)	Yes	21/43 (48.8)	0/44 (0.0)	0.000000014
	No	22/43 (51.2)	44/44 (100)	
4 to 14 units (n=30)	Yes	12/15 (80.0)	0/15 (0.0)	0.000010521
	No	3/15 (20.0)	15/15 (100)	
15 to 25 units (n=35)	Yes	5/17 (29.4)	0/18 (0.0)	0.019061584
	No	12/17 (70.6)	18/18 (100)	
>25 units (n=22)	Yes	4/11 (36.4)	0/11 (0.0)	0.090225564
	No	7/11 (63.6)	11/11 (100)	

Note: Stabilization was calculated between Baseline and 26 weeks after first dose.

[a] *P* values were calculated using Fisher's exact test.

Reference: Table 14.2.1.1

The table below shows the hemoglobin stabilization in the intention to treat population. In the Eculizumab treated group there were 21/43 patients who had hemoglobin stabilization compared to 0/44 patients with hemoglobin stabilization in the placebo group in the TRIUMPH study (P<<0.0001). In the Eculizumab group 22/43 patients did not achieve hemoglobin stabilization. When patients were stratified according to transfusion requirements prior to study entry, (low, intermediate and high strata) there was a statistically significantly greater number of patients who achieved hemoglobin stabilization treated with Eculizumab compared to placebo treated patients. The table below shows the results of the primary endpoint of hemoglobin stabilization in the intention to treat population.

Table 11. Summary of Units Transfused from Baseline to 26 Weeks (ITT)

Randomization strata	Eculizumab	Placebo	*P* value[a]
Overall (N)	43	44	<0.000000001
Mean (standard error)	3.0 (0.67)	11.0 (0.83)	
Median	0.0	10.0	
Range	(0.0, 16.0)	(2.0, 21.0)	
4 - 14 units (n)	15	15	0.000002311
Mean (standard error)	0.4 (0.29)	6.7 (0.72)	
Median	0.0	6.0	
Range	(0.0, 4.0)	(2.0, 12.0)	
15 - 25 units (n)	17	18	0.000665129
Mean (standard error)	4.2 (1.14)	10.8 (1.17)	
Median	2.0	10.0	
Range	(0.0, 15.0)	(2.0, 21.0)	
> 25 units (n)	11	11	0.000301977
Mean (standard error)	4.5 (1.59)	17.0 (1.04)	
Median	3.0	18.0	
Range	(0.0, 16.0)	(10.0, 20.0)	

[a] *P* values were calculated using Wilcoxon's rank sum test.

Reference: Table 14.2.1.2.1

In the SHEPHERD study the primary endpoint was the LDH AUC. The results of the analysis of the primary endpoint are shown in the table below. There was a significant decrease in the LDH AUC over time in these patients.

Table 9. Area Under the Curve for Lactate Dehydrogenase in U/L over time (PP)

Statistic	Eculizumab N=97	*P* Value[a]
Overall		<0.001
Mean (standard error)	-325375.7 (18296.43)	
Median	-301837.0	
Range	(-881796.5, -39392.5)	

Note: Area under the curve was calculated from Baseline to 26 weeks after first dose.

[a] Based on Wilcoxon signed rank test.

Reference: Table 14.2.1.1

Therefore, the TRIUMPH study was a randomized, double-blind, placebo-controlled, multicenter study of Eculizumab or placebo administered by IV infusion to 87 patients with hemolytic transfusion dependent PNH patients. The treatment arms were similar in terms of patient demographics, thrombosis and transfusion history. In this study hemoglobin stabilization (a co primary endpoint) was achieved in 48.8% of Eculizumab treated patients indicating that these patients did not require any transfusions during the 26 week study duration. Hemoglobin stabilization did not occur among any of the placebo patients and the difference between the treatment groups was a statistically significant. A sensitivity analysis performed on the

hemoglobin stabilization endpoints confirmed this efficacy outcome. After treatment with Eculizumab, statistically significant differences in hemoglobin stabilization were observed in the low and middle transfusion strata but not the high strata. In addition a statistically significant reduction in the number of packed red blood cell units transfused (a co-primary endpoint) was achieved in the Eculizumab group compared with placebo. During the 26 week study the median units transfused per patient was 0.0 in the Eculizumab group and 10.0 in the placebo group regardless of transfusion strata.

Secondary endpoint analyses for efficacy showed transfusion of avoidance was achieved in 22/43 Eculizumab patients and in no placebo patients which was statistically significant. The LDH AUC secondary endpoint analysis showed a statistically significant overall improvement in LDH AUC. Also, in each transfusion strata the LDH AUC improved after treatment with Eculizumab compared to the placebo group which was statistically significant. The sponsor analyzed the QOL in this study using the FACIT-Fatigue QOL tool. Eculizumab treated patients demonstrated statistically significant improvements in fatigue levels compared to placebo treated patients by visit six and at subsequent visits. However, because the QOL tool was administered to patients prior to transfusion without a follow-up QOL tool administration immediately after transfusion, is difficult to ascertain Eculizumab's effect on QOL independent of transfusion. The sponsor was asked to demonstrate that improvement in fatigue with Eculizumab did not require improvements in both hemolysis and anemia but was related to either the improvement in hemolysis without requirement for an improvement in anemia or a drug activity unrelated to the observed drug related improvements in hemolysis or anemia. The sponsor was able to demonstrate that Eculizumab is able to improve hemolysis which may positively impact on patient QOL.

The sponsor performed a series of exploratory endpoint analyses including the change of lactate dehydrogenase from baseline, an analysis of QOL using the EORTC QLQ-C30 tool, platelet activity, nitric oxide measure, free hemoglobin measurements and thrombosis. As is noted above, the change in lactate dehydrogenase from baseline, the analysis of QOL from the EORTC QLQ-C30 tool. In the TRIUMPH study, Eculizumab treated patients did show improvement in both the functional and symptom/item measures when assessed using the EORTC QLQ-C30 tool. In addition, nitric oxide measures and free hemoglobin measures favored the Eculizumab treated patients. The exploratory analysis for platelet activity by visit showed that there is no statistically significant change from baseline between the treatment groups.

Therefore it appears that Eculizumab is effective in stabilizing hemoglobin and decreasing the number of packed red blood cell transfusions required in transfusion dependent PNH patients. Secondary endpoint analyses for transfusion avoidance, LDH AUC and QOL measures using the FACIT- Fatigue tool support the fact that Eculizumab is effective in the treatment of PNH. Analyses of the effect of Eculizumab on the incidence of thrombosis are confounded by the fact that approximately 50% of patients in the Eculizumab treatment arm were on concomitant anticoagulant therapy.

In the open label SHEPHERD study, Eculizumab decreased the LDH AUC compared to baseline, appeared to improve quality of life as measured by the FACIT-F QOL instrument. Eculizumab treatment resulted in significant improvements in fatigue and hemolysis without

meaningful changes in transfusion requirements in the SHEPHERD study population. The sponsor stated that statistically significant improvements in fatigue were observed in the < four units per year pretreatment transfusion stratum. The sponsor indicated that this improvement in fatigue was obtained in patients with minimal pretreatment transfusion requirements and without demonstrable reductions in their transfusion requirements with Eculizumab treatment. The sponsor indicated that the baseline fatigue score for these patients (n=21) was 27.6. The mean change from baseline fatigue score at week 26 for these patients was 13.1 (P<0.001). In this group of 21 patients a median of 0.0 units of red blood cells were transfused during the 26 weeks pretreatment and a median of 0.0 units of packed red blood cells were transfused during the 26 weeks of treatment. Using the EORTC QLQ-C30 QOL tool, in an exploratory analysis, the sponsor was able to show that in patients treated with Eculizumab there were improvements in 13/15 measures including: global health status, role, social, cognitive, physical, emotional, fatigue, pain, dyspnea, appetite loss, insomnia, nausea/vomiting and diarrhea symptom domains. Conclusions regarding the effect of Eculizumab on thrombosis are confounded because of the fact that a majority of patients (59/97) were on concomitant anticoagulant therapy. The SHEPHERD study was designed primarily to assess the safety of Eculizumab in patients with PNH.

Therefore, it appears that Eculizumab is effective in the treatment of patients with transfusion dependent PNH by decreasing hemolysis which results in a stabilization of hemoglobin levels and avoidance of transfusion. It also appears that Eculizumab may improve QOL in patients with PNH in terms of decreasing fatigue and by improving other QOL parameters. Due to the fact that a large number of patients were on concomitant anticoagulant therapy a conclusion regarding Eculizumab's effect on thrombosis incidence rates cannot be made.

1.3.3 Safety

There were a total of 7 deaths in all of the Eculizumab studies combined. No deaths occurred in the TRIUMPH study. There were three deaths in non-PNH studies and four deaths in PNH studies other than the TRIUMPH study.

In the TRIUMPH study 4/43 patients in the Eculizumab group compared to 9/44 patients in the placebo group had serious adverse events. The most prevalent serious adverse event was exacerbation of PNH which occurred in one Eculizumab treated patient and three placebo treated patients.

In addition, overall one Eculizumab treated patient reported one serious adverse event associated with infection compared to four placebo patients who reported six infections related adverse events. Overall, there were three patients that developed meningococcal infection while enrolled in the Eculizumab trials. In the PNH trials there were two patients who discontinued treatment prematurely. Neither of these discontinuations appeared to be related to Eculizumab treatment (one patient with pregnancy, one patient with myelodysplastic syndrome).

The serious adverse events reported with Eculizumab treatment which had a frequency of more than 2% were headache (5.2%) and pyrexia (2.1%) in PNH studies. The sponsor reports that in uncontrolled studies the frequency of mild-moderate adverse events reported with Eculizumab

treatment was 99.0%. The overall frequency of severe treatment emergent adverse events in uncontrolled PNH studies was 22.8%. The sponsor states that adverse events reported as mild to moderate with Eculizumab treatment in more than 10% of patients in uncontrolled studies were: headache (47.7%), nasopharyngitis (39.9%), upper respiratory tract infection (28.5%), nausea (22.3%), arthralgia (17.6%), back pain (17.1%), diarrhea (17.1%), pyrexia (16.1%), vomiting (15.5%), dizziness (15.0%), cough (14.5%), pharyngeal pain (13%), influenza like illness (12.4%), extremity pain (12.4%), insomnia (11.9%), viral infection (11.4%), abdominal pain (11.4%), constipation (10.9%), urinary tract infection (10.9%) and constipation (10.9%).

In the PNH studies three patients developed human antihuman antibodies (HAHA) after treatment with Eculizumab. Two patients had IgG titers of 1:20 and one patient had IgM titers of 1:20 and 1:100. None of these patients developed a rebound in hemolysis despite the presence of these neutralizing antibodies.

Therefore, Eculizumab appears to be generally safe for the treatment of patients with PNH. However, because of the mechanism of action of Eculizumab on the immune system patients with PNH who are treated with Eculizumab are at increased risk for infections with encapsulated organisms. The sponsor proposes an early alert program and a registry program in order to minimize the risk of infections in patients with PNH were treated with Eculizumab. In addition patients who are to be treated with Eculizumab must be vaccinated with *Neisseria meningitidis* vaccine at least two weeks prior to treatment with Eculizumab as was described in the protocols in the PNH studies.

1.3.4 Dosing Regimen and Administration

The sponsor proposes an induction and maintenance phase for the administration of Eculizumab. In the induction phase, 600 mg of Eculizumab is administered every week for the first four weeks and 900 mg of Eculizumab is administered in week five. The maintenance phase consists of a 900 mg dose of Eculizumab every 14 +/- 2 days thereafter. The drug is administered as a [redacted] minute intravenous (IV) infusion.

1.3.5 Drug-Drug Interactions

No specific drug-drug interaction studies were performed in the Eculizumab clinical development program for PNH treatment.

1.3.6 Special Populations

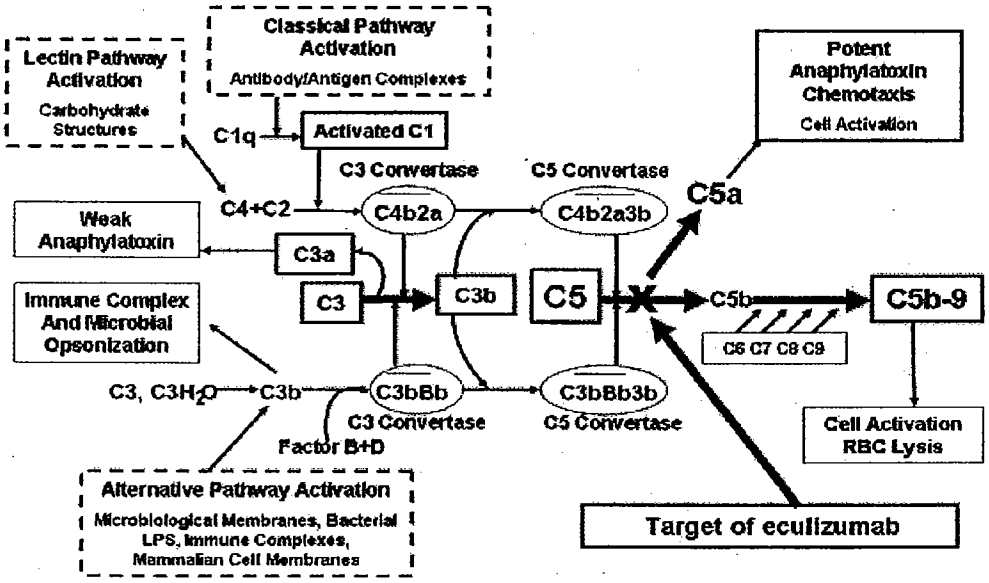
No studies were performed to analyze the safety and efficacy of Eculizumab in patient subgroups based on age, race or gender.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

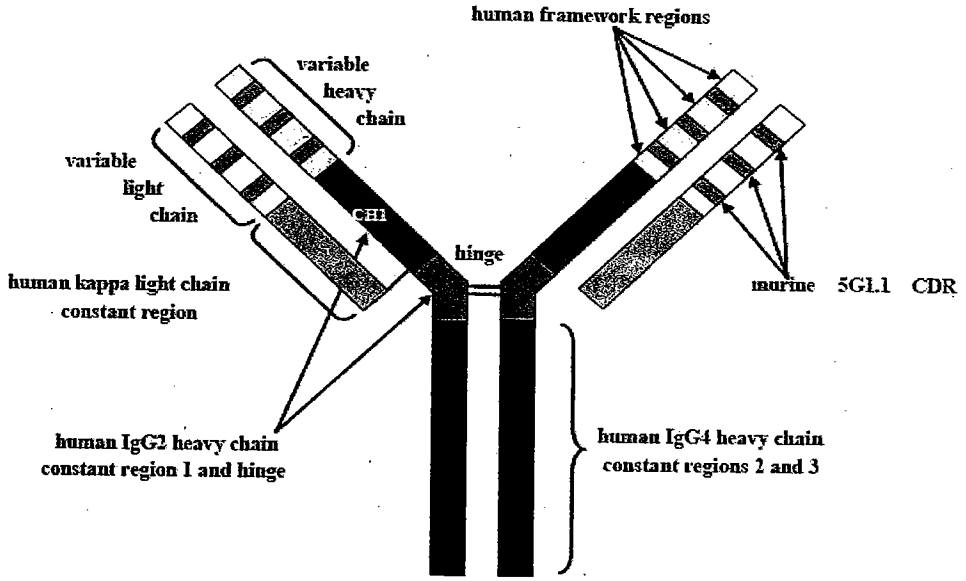
- Eculizumab is a humanized monoclonal antibody that binds to the human C5 complement protein. This results in the inhibition of the terminal complement cascade. CD 59 blocks the terminal complement cascade on normal red blood cells. Red blood cells lacking CD59 are type III red blood cell clones. Patients with paroxysmal nocturnal hemoglobinuria (PNH) lack CD59. The lack of CD59, on the red blood cells of patients with PNH allows the terminal complement cascade to hemolyze these red blood cells. The figure below shows the complement cascade and the target of Eculizumab.

Figure 2.5.1.4.2-1: The Complement Cascade



Eculizumab is an IgG kappa immunoglobulin comprised of human constant regions and murine complementarity determining regions (CDR) grafted onto human framework light and heavy chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa. The figure below shows the schematic diagram for Eculizumab.

Figure 2.5.1.1-1: Schematic Diagram of Eculizumab (h5G1.1 G2/G4 mAb)



- The established name is Eculizumab (h5G1.1 G2/G4 mAb). The proposed trade name is Soliris.
- Chemical class: New molecular entity biologic.
- Pharmacological class: Monoclonal antibody.
- Eculizumab was developed for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH). The drug is administered as a [redacted] minute intravenous (IV) infusion. The dosage regimen consists of an induction and maintenance phase. In the induction phase, 600 mg of Eculizumab is administered every week for the first four weeks and 900 mg of Eculizumab is administered in week five. The maintenance phase consists of a 900 mg dose of Eculizumab every 14 +/- 2 days thereafter. Eculizumab therapy was not studied in patients with PNH whose age was <18 years. Therefore, patients with PNH whose age is ≥ 18 years is the proposed treatment population.

2.2 Currently Available Treatment for Indication

PNH is an uncommon, life-threatening hemolytic anemia. The term "nocturnal" refers to the belief that hemolysis is triggered by acidosis during sleep and activates complement to hemolyze red blood cell that lack CD59. However, it is possible that any condition that activates complement could lead to a hemolytic crisis.[1] The disease is rare. The reported incidence is 1-2 per million. PNH is an acquired genetic terminal complement inhibitor deficiency disorder. The disease is characterized by chronic intravascular hemolysis. There is release of hemoglobin into the plasma from hemolyzed red blood cells. The hemolysis leads to anemia, thrombosis and fatigue - which are the most common morbidities for this disease. Clinically, the degree of the hemolysis is monitored by levels of lactate dehydrogenase (LDH). Currently there are no approved treatments for PNH. The following list is some of the treatments that have been tried for the treatment of PNH[2]:

- Transfusion for anemia with washed red blood cells in order to avoid transfusing complement in plasma.
- Oral iron therapy for iron deficiency.
- Steroid hormones:
  - Fluoxymesterone 20-30 mg orally daily.
  - Prednisone 20-60 mg orally every other day.
- Anticoagulants:
  - Prophylactic anticoagulation usually not indicated
  - Anticoagulant management of thrombotic complications with low molecular weight heparins, Coumadin has been used.
- Bone marrow transplantation.

2.3 Availability of Proposed Active Ingredient in the United States

Eculizumab is a new molecular entity (NME) and is not currently marketed in this country.

2.4 Important Issues with Pharmacologically Related Products

Currently there are no pharmacologically related products other than other monoclonal antibodies used in various other diseases. These monoclonal antibodies share the common adverse event of infusion reaction usually displayed as a hypersensitivity reaction either systemically or locally at the point of infusion. Also because this is a monoclonal antibody with human constant regions it is possible that anti-human neutralizing antibodies to Eculizumab may develop.

2.5 Presubmission Regulatory Activity

The regulatory history of Eculizumab is as follows:

- May 2003- BB IND 11075 for Eculizumab treatment of PNH submitted.
- August 2003 - Orphan drug designation granted.
- July 2004 - Special Protocol Assessment submitted and approved. The sponsor was told that the co primary endpoints would both need to show significant positive effects. In addition, the sponsor was told that a sensitivity analysis would need to be performed.
- July 2005 - Fast Track request submitted which identified hemolysis and decreased red blood cell transfusion as aspects that can benefit Eculizumab treated PNH patients. The request was denied due to the fact that the sponsor failed to show an unmet need and that no serious aspect of the serious disease PNH was identified.
- March 2006 - pre-BLA meeting held.
- September 15, 2006 - BLA submission.

2.6 Other Relevant Background Information

In October of 2003 the European Community orphan drug designation was granted. In November of 2004 the sponsor was given European Medicines Agency (EMeA) protocol assistance. In February of 2006 the EMeA gave the sponsor follow-up scientific advice on the quality of life endpoints. In June of 2006 the EMeA granted an Accelerated Assessment Procedure.

For this application the sponsor submits one randomized, double blind, placebo controlled multicenter study (C04-001, TRIUMPH, see section 4.1 of this review for description of study) and one open label study (C04-002, SHEPHERD see section 4.1 of this review for description of study). The original protocol for the TRIUMPH study was dated June 2, 2004. On August 8, 2004 an amendment to the protocol was implemented specifically for sites in Germany. This was done to address inclusion/exclusion regarding hepatitis and HIV status required by the German regulatory authorities. On August 10, 2004 a clarification letter was distributed to the primary investigators. This letter clarified the language in the protocol regarding hemoglobin sample collection times at transfusion visits, the removal of assays for gamma globulin, total cholesterol and triglycerides from the laboratory measurements, the inclusion of calculations for red blood cell indices and the addition of phosphorus to the blood chemistry list. These changes according to the sponsor did not alter the overall analysis plan. Of note, in the TRIUMPH study there was difference of one patient in the intention to treat (ITT) population compared to the per protocol population of patients. This patient (number 027-001) is not included in the ITT population because she was randomly assigned to treatment in error. Only two patients discontinued from treatment with Eculizumab in the TRIUMPH study. The sponsor did not conduct an analysis to assess the safety of Eculizumab in those patients who withdrew from the study, because such an analysis was considered to be not clinically meaningful.

The original protocol for the SHEPHERD study was submitted June 2, 2004. On November 24, 2004 an amendment to the protocol was implemented specifically for sites in Germany. This was done to address the inclusion/exclusion criteria regarding hepatitis and HIV status that the German regulatory authorities required prior to giving the protocol approval in that country. On September 23, 2004 an administrative letter was sent to the investigators to clarify discrepancies in the laboratory testing sections of the protocol. The wording for the testing sections in the protocol clarified testing for hepatitis and HIV. On March 4, 2005 protocol changes were made that included elimination of the upper limit for the number of transfusions required in the inclusion criteria, changing the intravascular hemolysis as measured by LDH AUC from a secondary endpoint to a primary surrogate of efficacy endpoint, changing the LDH change from baseline from an exploratory endpoint to a secondary endpoint and changing the [redacted].

For the SHEPHERD study the sponsor noted that protocol deviations involved incomplete study procedures, procedures or study visits outside of the prescribed visit window, laboratory samples collected at incorrect visits, infusion times exceeding protocol limits, incorrect infusion volumes and transfusions administered above the set point. Some study sites in Germany reported the PQ interval from patient electrocardiograms instead of the protocol specified PR interval. This was due to the standard used in Germany. In addition, patient 018-002 was granted a protocol

exemption from an inclusion criterion which stated that PNH patients had to have ≥ 10% type III red blood cell clones present by flow cytometry. Nevertheless, this patient was included because the primary investigator reasoned that the patient was hemolyzing extremely quickly and that the PNH clone could never build up to a 10% level. Patients 070-009, 070-012 and 070-013 were granted protocol exemptions from the inclusion criterion that required that patients have evidence of PNH for more than six months. Patient 015-001 received only 600 mg instead of the protocol specified 900 mg due to an error at the study site. Patients 022-002, 101-002, 102-003, 102-005, 092-002, 093-001 and 131-001 had visit number two outside the protocol prescribed 14 day window.

These protocol deviations and protocol amendments, in both the TRIUMPH and SHEPHERD studies, were good-faith changes and clarified the protocols. The patient errors listed appear to be minor and do not appear to affect the analysis of the safety and efficacy of Eculizumab in PNH patients reported by the sponsor.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

A number of CMC related concerns have been raised. Of particular note is that the sponsor has not provided adequate validation of their method for assessing the immunogenicity of Eculizumab these concerns are reflected in the postmarketing commitments listed in section 1.2.2 of this review.

3.2 Animal Pharmacology/Toxicology

Eculizumab does not inhibit C5 activity in the sera from 4 primate and 4 non-primate species. Tissue cross-reactivity of Eculizumab was evaluated by assessing binding to a panel of 38 human tissues. It was shown that Eculizumab binds to smooth and striated muscle as well as renal proximal epithelium. A 26 week mouse toxicity study with a surrogate antibody directed against murine C5 showed the blockage of hemolytic activity during the course of the study in both male and female mice. A no adverse effect level (NOAEL) was established at 60 mg/kg/week for maternal toxicity and reproductive performance and a NOAEL for embryo/fetal development toxicity was established at 30 mg/kg/week. The pharmacology/toxicology review of this submission stated there are no unresolved toxicology issues and from the perspective of nonclinical pharmacology and toxicology, Eculizumab is recommended for approval (see Pharmacology/Toxicology review completed February 27, 2007).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor submitted information from six clinical studies which provide the basis for establishing the safety and efficacy of Eculizumab therapy in PNH patients. The studies are listed in the table below.

Study Number	Phase/Design[1]	Duration/Status	Total Patients Enrolled
C02-001	2[3] / OL	12 weeks/Complete	11
E02-001	2[3] / OL (C02-001 Extension)	52 weeks/Complete	11
X03-001	2[3] / OL (E02-001 Extension)	104 weeks/Complete	11
C04-001	3 / R,DB,PC	26 weeks/Complete	87
C04-002	3 / OL	52 weeks/Ongoing 26 week Interim Complete	97
E05-001	3b / OL (C04-001, C04-002, and X03-001 Extension)	104 weeks/Ongoing	112[2] (~190 anticipated)

[1]R = Randomized; [2]As of July 18, 2006; [3]Also referred to as Phase I studies; DB = Double Blind; PC = Placebo Controlled; OL = Open Label.

The study C04-001, also known as the TRIUMPH study (A Hemoglobin Stabilization in Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab and Paroxysmal Nocturnal Hemoglobinuria Patients), is the pivotal study supporting Eculizumab's safety and efficacy for the treatment of PNH. For the TRIUMPH study the first patient's first visit was on August 27, 2004 and the last patient's last visit was on December 27, 2005. In addition, information from the open label study C04-002, also known as the SHEPHERD study (Safety in Hemolytic Paroxysmal Nocturnal Hemoglobinuria Patients Treated with Eculizumab: the Multicenter, Open Label, Research Design Study), was submitted by the sponsor to support the safety and also the efficacy of Eculizumab therapy in PNH patients. For the SHEPHERD study, the first visit of the first patient was on December 16, 2004 and the last patient's last visit was on March 21, 2006. An additional analysis of the safety of Eculizumab in PNH patients was undertaken using the combined safety database consisting of all of the PNH patients exposed to Eculizumab thus far in the clinical development program. The sponsor, in the submission, lists 196 PNH patients as having been exposed to Eculizumab. The sponsor reported in a teleconference on January 31, 2007 that one additional patient in a physician sponsored IND was exposed to Eculizumab that was not reported as part of the safety database for Eculizumab in the BLA submission. The non-PNH studies were reviewed to further analyze the safety database of Eculizumab.

In addition, the sponsor provided summaries of studies performed in the non-PNH setting which provides additional information for the safety of Eculizumab. The studies are listed in the table below.

Table 2.5.1.5-3: Listing of All Non-PNH Studies

Study Number	Indication	Phase/Design[1]	Duration/Status	Total Patients
C97-001-01	Rheumatoid Arthritis (RA)	1 / R, DB, PC	Single dose/Complete	42
C99-001	RA	2 / R, DB, PC	12 wks/Complete	209
E99-001	RA (C99-001 extension)	2 / OL	12 month/Complete	132
C00-003	Bullous Pemphigoid	2 / R, DB, PC	8 wks/Terminated	1
C01-004	RA	2 / R, DB, PC	12 month/Complete	367
E01-004	RA (C01-004 extension)	2 / OL	12 month/Complete	256
C97-002-01	Systemic Lupus Erythematosus	1 / R, DB, PC	Single dose/Complete	24
C99-004	Idiopathic Membranous Glomerulopathy (IMG)	2 / R, DB, PC	16 wks/Complete	117
E99-004	IMG (C99-004 extension)	2 / OL	12 month/Complete	72
C99-007	Psoriasis	2 / R, DB, PC	8 wks/Complete	40
C99-006	Dermatomyositis	2 / R, TP, PC	8 wks/Complete	13

[1]R = Randomized; DB = Double Blind; PC = Placebo Controlled; OL = Open Label.

4.2 Tables of Clinical Studies

See section 4.1.

4.3 Review Strategy

The medical review of the TRIUMPH and SHEPHERD studies is included in this document. The TRIUMPH and SHEPHERD studies were the primary studies used to understand the safety and efficacy of Eculizumab for the treatment of patients with PNH. Summaries of the other studies submitted by the sponsor to support Eculizumab's efficacy and safety in the treatment of patients with PNH were reviewed.

An additional analysis of the safety of Eculizumab in PNH patients was undertaken using the combined safety database consisting of all of the PNH patients exposed to Eculizumab thus far in the clinical development program. The sponsor in the submission lists 196 PNH patients as having been exposed to Eculizumab. The sponsor reported in a teleconference with the division in January of 2007 that one additional patient in a physician sponsored IND was exposed to Eculizumab that was not reported as part of the safety database for Eculizumab in the BLA submission. The non-PNH studies were reviewed to further analyze the safety database of Eculizumab.

4.4 Data Quality and Integrity

On September 26, 2006 the Division of Scientific Investigations (DSI) was consulted to evaluate one study site in Leeds, England (study site number 070, primary investigator Dr. Peter Hillman) and one study site in Washington, DC (study site number 027, primary investigator Dr. Neil Young) based on number of patients enrolled at each one of the sites. In addition, DSI also inspected the sponsor (Alexion Pharmaceuticals). PNH is a rare disease which is treated by a very limited number of physicians around the world. There were small numbers of patients enrolled at any one particular study site however, study site number 027 enrolled five patients and the site number 070 enrolled 12 patients. The results of the DSI audit are as follows:

- For the site number 027:
  - The investigator was found to have executed this study adequately. At this site 3/3 female subjects did not have month a year and pregnancy tests during the screening, observation and treatment phase as required by the protocol for the TRIUMPH study.
  - 1/3 subjects was administered one incorrect dose investigational drug (180 mL instead of 120 mL) as required by the protocol for the TRIUMPH study.
  - 1/3 subjects was not given rescue medication on the date of first investigational drug infusion. This patient received rescue medication seven days after the first investigational drug infusion.
  - Overall it appeared that the data collected and generated was acceptable.

- For the site number 070:
  - There did not appear to be any significant deviations from regulations and the study was conducted according to the TRIUMPH study protocol.

- For the sponsor investigation:
  - The inspection evaluated the sponsor's documentation of selection of qualified investigators for the study, financial disclosures and trading of clinical investigators. The inspection verified that the sponsor followed up on all problems encountered.

Therefore, the violations noted above appear to be inconsequential to this review.

4.5 Compliance with Good Clinical Practices

All studies, both in the PNH setting and non-PNH setting, were conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practices and local regulatory requirements. The protocols and any amendments were approved by an institutional review board prior to initiation and continuation of the studies. Written informed consent provided by the patient was required and the written informed consent form for the TRIUMPH study was reviewed. The informed consent, protocol violations and site-specific issues were reviewed and found to be within accepted standards.

4.6 Financial Disclosures

The [redacted] study's primary investigator was [redacted] The sponsor reported that an unrestricted educational grant was awarded to the [redacted] in the amount of £50,000 annually. The grant was used to fund the salary of a research fellow. In addition, the sponsor reported that a two-year unrestricted educational grant was awarded to the [redacted] which is affiliated with [redacted] in the amount of £50,000 annually. The sponsor reports that the grant was used to fund the salary of a research fellow under the direction of Dr. [redacted] The financial disclosures appear to be appropriate.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Eculizumab is administered IV and has an assumed 100% bioavailability. The distribution is expected to be typical of the endogenous human antibodies within the vascular and extracellular spaces. Population pharmacokinetic modeling with Eculizumab shows that the volume of distribution approximates that of plasma. The sponsor states that the amount of Eculizumab associated with non-C5 plasma proteins and the effects of plasma protein binding on Eculizumab distribution have not been determined. Eculizumab contains only naturally occurring amino acids and has no known active metabolites. Human antibodies are metabolized by lysosomal enzymes to small peptides and amino acids. The extent of catabolism is inversely proportional to the receptor binding affinity. No specific clinical studies have been conducted to evaluate specific pathways of Eculizumab excretion. Due to its molecular size (148 kD) Eculizumab like other immunoglobulins is expected to be excluded from filtration by normal kidneys. However, in animal studies, testing with the parent molecule for Eculizumab showed that this parent molecule can cross the placental barrier. The table below shows a summary of the single-dose and multiple-does pharmacokinetic parameters of serum Eculizumab estimated from a rheumatoid arthritis model. This model appears to adequately have described the pharmacokinetics of Eculizumab in patients with PNH. The sponsor reports that no clinically important covariates with respect to pharmacokinetic parameters were found. No accumulation of Eculizumab was observed.

Table 9.5 C04-001 Parameter Mean Estimates 1C-p Method (n=40)

	CL (mL/hr/kg)	V_d (mL/kg)	K_{el} (1/hr)	$t_{1/2}$ (hr)
Mean	0.311183	110.3	0.002776	271.7
SD	0.125097	17.9	0.000817	81.6
% SD	40.20	16.2	29.45	30.0
Min	0.150944	79.1	0.001376	134.1
Max	0.745052	144.1	0.005169	503.8
Median	0.289969	108.3	0.002793	248.2

1C-p = 1CPNCLI; 1-compartment clearance parameterization IT2B method
Source: Appendix 15

5.2 Pharmacodynamics

The sponsor states that 35 mcg/ml of Eculizumab blocks the terminal complement mediated intravascular hemolysis in PNH patients. Pharmacodynamics of Eculizumab mediated complement inhibition was measured in human serum samples using an assay of antibody sensitized chicken erythrocyte lysis in the presence of human serum complement, in which even small amounts of unbound C5 resulted in > 90% hemolysis. The sponsor states that Eculizumab binds to human C5 and inhibits human C5 cleavage in a dose-dependent manner such that a 1:1 molar ratio of Eculizumab to C5 is sufficient for C5 inhibition. The sponsor states that there are no known secondary pharmacological effects of Eculizumab because of the highly specific interaction of Eculizumab with its target as indicated by the lack of Eculizumab binding to C5 from other species.

5.3 Exposure-Response Relationships

Eculizumab administered in a 30 minute IV infusion at doses > 4 mg/kg or at fixed doses > 600 mg reaches peak serum concentrations in excess of 100 mcg/ml within one hour of infusion. At these doses of Eculizumab terminal complement inhibition is evidenced by the essentially complete inhibition of complement mediated hemolysis. The sponsor notes that the hemolysis in pharmacodynamic assays is inhibited by Eculizumab concentrations in excess of 35 mcg/ml. Concentrations below this threshold result in inadequate inhibition of C5. This takes place at concentrations < 20 mcg/ml as measured by the pharmacodynamic hemolytic assay. The sponsor states that the proposed dosing regimen effectively maintains the concentration of Eculizumab at approximately 35 mcg/ml. The sponsor states that no clinically relevant pharmacodynamic interactions between Eculizumab and other medications or substances have been observed in any of the clinical subjects at this point. The sponsor also states that, with the exception of patients with a known C5 deficiency, no genetic factors have been identified that would be anticipated to affect the response to Eculizumab. The pharmacology group in the Division of Medical Imaging and Hematology stated that the pharmacology of Eculizumab is

described by the sponsor is appropriate and reflects the pharmacologic parameters of Eculizumab.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for Eculizumab in this submission is: "Eculizumab is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH)."

6.1.1 Methods

The clinical data upon which this application is submitted is based on the TRIUMPH study with additional support from the SHEPHERD study.

6.1.2 General Discussion of Endpoints

The TRIUMPH study was a randomized, double-blind, placebo-controlled, multicenter study of Eculizumab or placebo administered IV to patients with PNH. The primary objective of this study was to evaluate the safety and efficacy of Eculizumab in transfusion dependent patients with hemolytic PNH. The efficacy co-primary endpoints for this study were hemoglobin stabilization and the number of packed red blood cell units transfused during the treatment phase of the study through 26 weeks. The secondary objectives of this study were transfusion avoidance, hemolysis as measured by lactate dehydrogenase (LDH) area under the curve (AUC) during the treatment phase from baseline through 26 weeks. This study also had the exploratory endpoints of LDH change from baseline through 26 weeks, EORTC QLQ-C30 quality-of-life (QOL) changes from baseline through 26 weeks, thrombosis, platelet activity, nitric oxide and free hemoglobin measures from randomization and through 26 weeks.

The SHEPHERD study was an open label, multicenter study of Eculizumab administered IV to patients with PNH for 52 weeks. The primary objective of this study was to evaluate the safety of Eculizumab in patients with transfusion dependent PNH. The secondary objectives of this study were to analyze hemolysis reduction as measured by LDH AUC and changes in the functional assessment of chronic illness therapy fatigue (FACIT-F QOL) scale. Exploratory endpoints for this study included health-related QOL as measured by the EORTC QLQ-C30 and measures of thrombosis, platelet activity, nitric oxide and free hemoglobin.

6.1.3 Study Design

The TRIUMPH study was a randomized, double-blind, placebo-controlled, multicenter study of Eculizumab or placebo administered IV to patients with PNH. Patients that were randomized to the placebo group received placebo IV once a week for five doses then once every two weeks for 21 weeks. Patients randomized to the Eculizumab group received Eculizumab as noted in section 2.1 of this review. Patients who completed the study received 16 IV infusions. The

duration of the study was as follows, a 12 week enrollment phase followed by a 13 week observation phase followed by a 26 week treatment phase and an 8 week post-treatment phase. The sponsor supplied the study drug and placebo. Patients who were prematurely discontinued from the study had follow-up contact through 12 weeks after their last dose. 87 patients were enrolled in the study. Patient stratification was based on packed red blood cell transfusions within one year prior to screening. The strata were as follows:

- 4-14 units (low stratum).
- 15-25 units (mid stratum).
- > 25 units (high stratum).

The major inclusion criteria were as follows:

- Male or Female patients had to be at least 18 years of age.
- Required to have transfusions and 12 months prior to visit number one.
- CD 59 cell clone ≥ 10%.
- Stable dose of erythrocyte stimulating agent (ESA) for 26 weeks prior to screening visit number one with a dose remaining stable during the observation and treatment phases.
- Immunosuppressive therapy it was to be stable for at least 26 weeks prior to the first visit and was to remain stable during the observation and treatment phases.
- Corticosteroid dose was to be stable for at least four weeks prior to the first visit. The dose could remain stable or decrease over the course of the study.
- Anticoagulant therapy was to be stable for four weeks with international normalized ratio (INR) remaining stable during the observation and treatment phases.
- Iron supplementation or folic acid was to be stable for four weeks prior to visit number three.
- Vaccination against *Neisseria meningitidis* at least 14 days prior to visit number three.

In addition, during the observation period following inclusion criteria were applied:

- Documented LDH level ≥ 1.5 times the upper limit of normal either at visit one or during the observation phase.
- Patients that received red blood cell transfusion during the observation phase if the patients hemoglobin was≤ 9 g/dl with symptoms or if the hemoglobin was ≤ 7 g/dl without symptoms, and also within a 1.5 g/dl of the mean hemoglobin pretransfusion value for the previous 12 months. The transfusion was to be carried out in accordance with the patient's individual transfusion hemoglobin algorithm and was to occur within 48 hours a hemoglobin sample that predicted the transfusion.
- Platelet count ≥ 100,000/mcl either at visit one or during the observation phase.

The exclusion criteria for this study were as follows:

- Mean hemoglobin level prior to transfusion over the previous 12 months > 10.5 g/dl.
- Absolute neutrophil count ≤ 500/mcl.
- Presence or suspicion of bacterial infection.

- Known or suspected hereditary complement deficiency.
- Pregnant, breast-feeding or intending to conceive during the course of the study including the post-treatment phase.
- History of meningococcal disease.
- History of bone marrow transplantation.

Patients were to be discontinued from treatment for the following reasons:

- If ≥ 25% absolute decrease in PNH red blood cell clone population in one week or less.
- The hemoglobin level was ≤ 5 gm/dl.
- There was a change in mental status.
- There was a 50% increase in serum creatinine.
- Thrombosis developed.
- If the patient was discontinued from treatment then blood transfusion, exchange transfusion, anticoagulant therapy or steroid treatment could be administered at the discretion of the treating physician.

The schedule of events for this study is listed in the tables below.

Table 2. Schedule of Events

STUDY PHASE	Enrollment		Treatment																	Post-treatment	
Study Period	Observation Period		Induction Period						Maintenance Period										Unscheduled		
Study Month	Screen	Month -3 to 0	Month 1				Month 2		Month 3		Month 4		Month 5		Month 6		Month 7			FINAL	
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	D	Weeks	
Study Week			0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26		1-8	ET
Informed consent	X																				
Demographics	X																				
Medical, transfusion, and thrombosis history	X																				
Physical examination	X																	X			X
Weight	X		X															X			X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review laboratory results		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram	X		X						X									X	X	X	X
Blood and urine	X	X	X	X	X	X	X	X	X		X	X	X		X		X	X		X	X
Lactate dehydrogenase	x	x	x	x	x	x	x		x		x		x		x		x	x			x
Hematology and chemistry	x	x	x		x		x		x		x		x		x		x	x			x
Reticulocyte count	x	x	x		x		x		x		x		x		x		x	x			x
Haptoglobin	x	x	x		x		x		x		x		x		x		x	x			x
Urinalysis	x	x	x		x		x		x		x		x		x		x	x			x
Hemoglobin and serum creatinine																				x	
Pharmacokinetics/pharmacodynamics			B	T/P			T/P	T/P			T/P							T/P			T
Coagulation profile	x		x						x									x			x

Table 2. Schedule of Events

STUDY PHASE	Enrollment		Treatment																	Post-treatment	
Study Period	Observation Period		Induction Period						Maintenance Period										Unscheduled		
Study Month	Screen	Month -3 to 0	Month 1				Month 2		Month 3		Month 4		Month 5		Month 6		Month 7			FINAL	
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	D	Weeks	
Study Week			0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26		1-8	ET
Flow cytometry for PNH red blood cells, white blood cells, and platelet clone size	x		x						x									x		x	x
Platelet activity assays	x			x	x		x					x						x			x
Free hemoglobin/NO measures	x			x	x		x					x						x			x
Pregnancy (β-human chorionic gonadotropin)	x																	x			x
Anti-h5G1.1-mAB (HAHA)			x								x							x			x
Ferritin, vitamin B_{12}, folate			x															x			x
Meningococcal vaccine titer given/assayed	x	x#																x			x
Complete transfusion algorithm worksheet	X																				
Administer quality-of-life instruments		X^	X	X	X	X	X				X				X			X			X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thrombosis record (MAVE)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vaccination for Neisseria meningitidis	X*																				
Prescribe rescue antibiotic and provide identification card			X																		
Review entry criteria / fax attestation form for authorization to randomize		X**																			
Call IVRS for randomization		X																			

Table 2. Schedule of Events

STUDY PHASE	Enrollment		Treatment																	Post-treatment	
Study Period	Observation Period		Induction Period						Maintenance Period										Unscheduled		
Study Month	Screen	Month -3 to 0	Month 1				Month 2		Month 3		Month 4		Month 5		Month 6		Month 7			FINAL	
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	D	Weeks	
Study Week			0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26		1-8	ET
Dosing visits (all visits are ±2 days); Dose (mg)			600	600	600	600	900	900	900	900	900	900	900	900	900	900	900	900			
Transfusion record update (date and # of PRBCs)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ET =Early Termination; B=Baseline T/P=Trough and Peak T=Trough NO=nitric oxide HAHA =human antihuman antibody MAVE=major adverse vascular event
IVRS=interactive voice response system

*Patients must have been vaccinated for *N meningitides* 14 days prior to randomization at Visit 1 or during the observation period as determined by the principal investigator's discretion

^The quality-of-life assessment was to be done before the patient was given a transfusion.

#The meningococcal vaccine titer assay sample was to be collected 4 to 8 weeks postvaccination.

**Prior to calling IVRS for randomization, written authorization to randomly assign a patient to treatment must have been received from [redacted] global project manager or Alexion's clinical project manager.

In addition safety assessments included treatment emergent adverse events, clinical laboratory and electrocardiogram data as well as vital signs were to be analyzed. Adverse events were assigned MedRA preferred terms and tabulated as incidence rates per treatment group. The safety review for this study can be found in section 7 of this review.

The statistical analysis was as follows:

- Patient characteristics at baseline were summarized for each treatment group. Summary statistics were used to present the demographics, transfusion history, thrombosis history and LDH. The number of study drug infusions and total amount of study drug infused

were summarized by treatment group. The frequency and listings of concomitant medications were also provided by the sponsor.

- The co primary endpoints and all secondary endpoints of the primary analysis were based on the intention to treat (ITT) population. The hemoglobin set point for each patient was defined as ≤ 9 g/dl in patients with symptoms and was ≤ 7 g/dl in patients without symptoms. To achieve a designation of hemoglobin stabilization, a patient had to maintain a hemoglobin concentration above the hemoglobin set point and avoid any red blood cell transfusion for the entire 26 week treatment period. Patients who reached or dropped below their predetermined hemoglobin set point did not achieve hemoglobin stabilization. Those patients who withdrew prematurely from the study or work transfused above their hemoglobin set point during the treatment phase also were treated as not achieving hemoglobin stabilization. A 2-sided Fisher exact test was used for analysis. Each patient's units of packed red blood cells transfused after randomization through visit 18 were calculated. For those patients who discontinued study drug but remained in the study for follow-up the actual transfusion records were used to calculate the units transfused. For patients who had at least one transfusion but withdrew prematurely from the study prior to 26 weeks, the number of units were prorated by a applying the formula (26/number of weeks on study drug) x (Number of units transfused while on the study drug). For patients who withdrew prematurely from the study prior to having a transfusion their transfusion data, 26 weeks previous to their last contact date, was used to calculate the number of units of packed red blood cells transfused. The primary analysis method was the Wilcoxon rank sum test. A sensitivity analysis was performed based on the following rules in order to test the robustness of the results for the co primary endpoints:

    - If a patient assigned to placebo violated the protocol by receiving a transfusion without meeting the hemoglobin transfusion criteria, that transfusion was ignored in determining the endpoints and the patient was considered to have achieved hemoglobin stabilization.
    - If a patient assigned to Eculizumab violated the protocol by receiving a transfusion without meeting the transfusion criteria, that transfusion was counted in determining the endpoints and the patient was not considered to have achieved hemoglobin stabilization.

For the sensitivity analysis the population in each treatment group for packed red blood cell transfusion units at visit 18 was examined. For each treatment group, available packed red blood cell transfusion unit values were used to impute missing data using multiple imputation, mean values and median values.

The secondary efficacy analyses were undertaken as follows:

- The endpoint of transfusion avoidance was classified for each patient during the 26 week treatment phase I utilizing patients' transfusion records from randomization through visit 18. Those patients who withdrew prematurely from the study during the treatment phase were treated as requiring transfusion. The analysis was carried out using the two sided Fisher exact test.

- The AUC of LDH from baseline through visit 18 was calculated for each patient. For patients with missing LDH values, the last observation carried forward method was used to impute missing values. The AUC was analyzed using the Wilcoxon rank sum test.
- The scoring guideline for the FACIT-Fatigue scale was used to calculate the fatigue score. The main hypothesis of interest was that Eculizumab will provide a statistically significant increase in a patients' total FAC IT-Fatigue scale score compared to placebo. The change in the total FAC IT-Fatigue score from baseline was analyzed using a mixed effects model with baseline as covariate, treatment and time as fixed effects and patient as a random effect.

The SHEPHERD study was an open label, multicenter study of Eculizumab administered IV to 97 patients with transfusion dependent hemolytic PNH. Patients who received the same dosing regimen and schedule of Eculizumab as that of the TRIUMPH study. This study had a 12 week enrollment phase followed by a two-week screening phase followed by a 52-week treatment phase and an eight week post-treatment phase. Patients who prematurely discontinued study drug were required to have for follow-up visits at 1, 2, 4 and 8 weeks after their last dose of study drug and a follow-up contact 12 weeks after their last dose of study medication. The inclusion and exclusion criteria were similar to that of the TRIUMPH study with the exception of the following:

- TRIUMPH
  - $\geq$ 4 transfusions/12m
  - $\geq$ 100,000/mcl platelets
  - $\geq$ 1.5 ULN LDH
  - $\geq$ 10% RBC clone
- SHEPHERD
  - $\geq$ 1 transfusions/24m
  - $\geq$ 30,000/mcl platelets
  - $\geq$ 1.5 ULN LDH
  - $\geq$ 10% RBC clone

Therefore, the SHEPHERD study patient population had a broader range of transfusion requirements and degree of thrombocytopenia which is reflected in the demographics for the SHEPHERD study.

The SHEPHERD study had similar discontinuation from treatment criteria to that of the TRIUMPH study. The schedule of events for the SHEPHERD study is shown below.

Table 2. Schedule of Events

Study Period: Weeks: -2 to 26	Screen	Induction Period					Maintenance Period										
Study Week	-2	0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Informed consent	X																
Demographics	X																
Medical, transfusion, and thrombotic history	X																
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X																
Weight	X	X															
Review laboratory results		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X							X									X
Blood and urine collection	X	X	X	X	X	X	X	X		X	X	X		X		X	X
Hematology and chemistry	x	x		x		x		x		x		x		x		x	x
LDH	x	x	x	x	x	x		x		x		x		x		x	x
Reticulocyte count	x	x		x		x		x		x		x		x		x	x
Haptoglobin	x	x		x		x		x		x		x		x		x	x
Urinalysis	x	x		x		x		x		x		x		x		x	x
Hemoglobin and serum creatinine																	
Blood and urine collection																	
Flow cytometry for PNH RBC, WBC, and platelet clone size (refer to protocol, section 6 text)	x							x									x
Coagulation profile	x							x				x					x
Pregnancy (β-HCG)	x																
Ferritin, vitamin B12, folate		x															x

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Table 2. Schedule of Events

Study Period: Weeks: -2 to 26	Screen	Induction Period					Maintenance Period										
Study Week	-2	0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Anti-h5G1.1-Mab (HAHA)		x				x											x
Blood and urine collection																	
PK/PD		B	T/P			T/P	T/P			T/P							T/P
Platelet activity assays		x	x	x		x					x						x
Free hemoglobin/NO measures		x	x	x		x					x						x
Meningococcal vaccine titer assays	x							x									x
Administer QoL	X	X	X	X	X	X				X				X			X
Thrombosis record (MAVE)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vaccination: N meningitidis*	X																
Prescribe rescue antibiotic and provide identification card		X															
Review entry criteria and fax patient confirmation form	X																
Register patient via IVRS	X																
Dosing visit ±2 days																	
Dose (mg)		600	600	600	600	900	900	900	900	900	900	900	900	900	900	900	900
Transfusion record update		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

B = baseline; ET = early termination; IVRS = interactive voice response system; T/P = trough and peak

* Patients must have been vaccinated for *Neisseria meningitidis* 14 days prior to receiving eculizumab; he/she may have been vaccinated at Visit 1 or as determined at the discretion of the principal investigator

^ The QoL assessment should have been done before the patient was transfused

WEEK 28 TO END OF STUDY CONTINUED ON THE NEXT 2 PAGES

Table 2. Schedule of Events (continued)

Study Period: Weeks 28 to Posttreatment															Post-Trt Phase	
Study Week	28	30	32	34	36	38	40	42	44	46	48	50	52	Unscheduled	WKS	
Study Visit	18	19	20	21	22	23	24	25	26	27	28	29	30		1-8	ET
Informed Consent																
Demographics																
Medical, transfusion, and thrombosis history																
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination													X			X
Weight													X			X
Review laboratory results	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG							X						X			X
Blood and urine collection	X		X		X		X		X		X		X		X	X
Hematology and chemistry	X		X		X		X		X		X		X			X
LDH	X		X		X		X		X		X		X			X
Reticulocyte count	X		X		X		X		X		X		X			X
Haptoglobin	X		X		X		X		X		X		X			X
Blood and urine collection																
Urinalysis	X		X		X		X		X		X		X			X
Hemoglobin and serum creatinine															X	
Flow cytometry for PNH RBC, WBC, and platelet clone size (refer to protocol, section 6 text)							X						X		X	X
Coagulation profile			X				X				X		X			X
Pregnancy (β-HCG)													X			X

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Table 2. Schedule of Events (continued)

Study Period: Weeks 28 to Posttreatment															Post-Trt Phase	
Study Week	28	30	32	34	36	38	40	42	44	46	48	50	52	Unscheduled	WKS	
Study Visit	18	19	20	21	22	23	24	25	26	27	28	29	30		1-8	ET
Ferritin, Vitamin B12, folate													X			X
Anti-h5G1.1-Mab (HAHA)							X						X			X
Blood and Urine Collection																
PK/PD													T/P			T
Platelet activity assays													X			X
Free hemoglobin/NO measures													X			X
Meningococcal vaccine titer assays													X			X
Administer QoL[a]					X				X				X			X
Thrombosis record (MAVE)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dosing Visit ±2 days																
Dose (mg)	900	900	900	900	900	900	900	900	900	900	900	900	900			
Transfusion record update	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

B = baseline; ET = early termination; ; IVRS = interactive voice response system; T/P = trough and peak

[a] Patients must have been vaccinated for *N meningitidis* 14 days prior to receiving eculizumab; he/she may have been vaccinated at Visit 1 or as determined at the discretion of the Principal Investigator

[b] The QoL assessment should have been done before the patient was transfused.

In addition safety assessments included treatment emergent adverse events and clinical laboratory and vital signs were to be analyzed. Adverse events were assigned MedRA preferred terms and tabulated as incidence rates per treatment group. The safety review for the TRIUMPH, SHEPHERD and combined studies can be found in section 7 of this review.

Two populations were analyzed for the TRIUMPH study - the per protocol population and the safety population. The criteria for patient analysis subsets were, in the per protocol population,

all patients who received any amount of Eculizumab and had no major protocol violations and in the safety population, any patient who received any amount of Eculizumab was considered evaluable for safety analyses. The LDH AUC change from baseline to week 26 was calculated and sensitivity analyses performed. QOL measurements were calculated and analyzed at 26 weeks. The incidence of thrombosis was tabulated for each type of event. In addition platelet activity was analyzed that 26 weeks taking into account patient's transfusions and concomitant medications such as anticoagulants. Changes of platelet activity results from baseline were analyzed using a mixed- effects model. Changes in nitric oxide and free hemoglobin measures from baseline were also analyzed using a mixed - effects model. Safety was assessed by examination of treatment emergent adverse events and analyses were performed at 26 weeks. Adverse events were assigned MedRA preferred terms and tabulated by severity and analyzed using descriptive statistics. In addition adverse events related to the occurrence of infection were tabulated. Descriptive statistics were used in the analysis of laboratory safety data.

The design of the TRIUMPH study appears to be appropriate for the evaluation of safety and efficacy. However, the SHEPHERD study was an open label study and lacked a comparator. The sponsor used baseline patient data in terms of LDH AUC, QOL, transfusion history and other laboratories which were analyzed. Therefore the TRIUMPH study is the pivotal study supporting the safety and efficacy of Eculizumab for the treatment of patients with PNH. Efficacy data from the SHEPHERD study is supportive. The SHEPHERD study was designed to evaluate safety primarily.

6.1.4 Efficacy Findings

In the TRIUMPH study, 114 patients were screened and five patients did not meet entry criteria. One patient revoked consent. There were 109 patients who were enrolled in the study however, one patient did not meet enrollment criteria. There were 108 patients who entered the observation phase of which 20 were not eligible for treatment. Therefore, 88 patients were randomized of which, one patient was removed from the analysis because they were randomized in error. 87 patients entered the treatment phase and two patients terminated their participation early. 85 patients completed all visits. 10 patients discontinued treatment but completed all study visits. 75 patients completed the treatments as scheduled. The disposition of the patients by treatment group for the ITT population is shown below.

Table 3. Patient Disposition by Treatment Group (ITT)

	Eculizumab N = 43 n (%)	Placebo N = 44 n (%)	Total N = 87 n (%)
Completed treatment	41 (95.3)	34 (77.3)	75 (86.2)
Discontinued treatment because of:			
Lack of efficacy	0 (0.0)	10 (22.7)	10 (11.5)
Treated and terminated early because of:			
Patient requested withdrawal	1 (2.3)	0 (0.0)	1 (1.1)
Adverse event	1 (2.3)	0 (0.0)	1 (1.1)

Reference: Table 14.1.1.1

In the TRIUMPH study, protocol deviations in individual patients do not appear to change the efficacy results. Patient 010-001 who was treated with Eculizumab did not have a serum pregnancy test at screening as required per protocol. This site performed a urine dipstick test. Patient 010-001 eventually had a serum beta hCG pregnancy test but not until the last visit on study. Patient 102-002 also treated with Eculizumab did not have a serum beta hCG pregnancy test performed on till visit number three. Both of these patients were randomized in violation of the protocol. Patient 028-003 reported her pregnancy to the primary investigator on the [redacted] She had been randomly assigned to Eculizumab treatment on [redacted] and received her first dose on [redacted]. When her pregnancy was reported the patient was discontinued from the study drug. This patient's pregnancy resulted in a normal pregnancy despite Eculizumab exposure. Patient 028-002 was randomly assigned to Eculizumab treatment however it was discovered that after randomization she had not been vaccinated. She did not receive her first dose on till she was vaccinated after 14 days and had another qualifying transfusion. Patient 027-001 did not meet entry criteria (the mean hemoglobin was below the specified protocol criterion) but was inappropriately entered for random assignment to treatment. The patient did not receive study drug. The sponsor made a decision to not include this patient in the intention to treat population because she was randomly assigned in error. Patient 015-002 was taking erythropoietin on February 17, 2005. The protocol required that patients on ESA had to have any stable dose for at least 26 weeks prior to visit number one. At visit number one the investigator indicated that the ESA did not appear to improve the patient's status and the ESA was subsequently discontinued. The sponsor reported that the patient had an increased need for transfusion in the first several weeks of the study. The patient was allowed to remain in the study and completed all study assessments. Seven patients (013-0 02, 0 to 7-004, 061-002, 070-005, 070-010, 101-002 and 102-003) showed a discrepancy between the stratification assignment as entered compared to the number of units transfused in the patient's transfusion history. All analyses for this study were performed on the intention to treat population as randomized and stratified according to the parameters listed above. Patient 015-001 who was treated with placebo was not on a stable dose of prednisone for weeks prior to randomization. The patient was allowed to stay in the study.

The demographic and baseline characteristics for the intention to treat population are summarized in the table below.

Table 4. Summary of Demographics and Baseline Characteristics (ITT)

	Eculizumab N = 43	Placebo N = 44	*P* Value[b]
Gender n (%)			
Male	20 (46.5)	15 (34.1)	0.2783
Female	23 (53.5)	29 (65.9)	
Race n (%)			
Not required[a]	1 (2.3)	1 (2.3)	0.2629
Caucasian	37 (86.0)	41 (93.2)	
Black	4 (9.3)	0 (0.0)	
Asian	1 (2.3)	1 (2.3)	
Other	0 (0.0)	1 (2.3)	
Age (years)			
Mean (standard deviation)	42.1 (15.47)	38.4 (13.38)	0.2714
Median (first, third quartile)	41.0 (29.0, 51.0)	35.0 (29.0, 45.0)	
Range	(20.0, 85.0)	(18.0, 78.0)	
Age groups (years) n (%)			
<65	37 (86.0)	42 (95.5)	0.2085
65 to 75	5 (11.6)	1 (2.3)	
≥75	1 (2.3)	1 (2.3)	
Weight (kg)			
n	41	43	0.2287
Mean (standard deviation)	74.9 (11.69)	72.8 (14.04)	
Median (first, third quartile)	76.1 (65.6, 83.7)	70.0 (61.5, 79.6)	
Range	(53.1, 102.0)	(55.0, 124.1)	
Height (cm)			
n	42	44	0.6750
Mean (standard deviation)	170.4 (9.37)	169.7 (8.89)	
Median (first, third quartile)	171.5 (164.0, 179.0)	168.0 (162.3, 175.5)	
Range	(151.0, 187.0)	(156.0, 189.0)	
Blood type n (%)			
A-	5 (11.6)	1 (2.3)	0.1357
A+	11 (25.6)	20 (45.5)	
B-	2 (4.7)	0 (0.0)	
B+	3 (7.0)	5 (11.4)	
AB+	2 (4.7)	2 (4.5)	
O-	4 (9.3)	6 (13.6)	
O+	16 (37.2)	10 (22.7)	

[a] Local law did not allow the collection of race data at sites in France.

[b] For categorical variables, exact Pearson's chi-square test was used, and for continuous variables, Wilcoxon's rank sum test was used.

Reference: Table 14.1.1.2

The two arms of the study were overall well-balanced in terms of the patient demographics listed in the table above. The transfusion history for the patients in the ITT population is presented in the table below. Overall, the two arms of the study were well-balanced in terms of the transfusion history.

Table 6. Transfusion History (ITT)

Parameter	Eculizumab N = 43	Placebo N = 44
Mean hemoglobin prior to transfusion		
n	43	44
Mean - g/dL (standard deviation)	8.0 (0.86)	7.9 (1.02)
Median - g/dL (first, third quartile)	8.1 (7.3, 8.5)	7.8 (7.2, 8.6)
Range - g/dL	(5.9, 9.8)	(6.0, 10.5)
Mean hemoglobin posttransfusion		
n	10	8
Mean - g/dL (standard deviation)	10.5 (1.06)	9.0 (1.22)
Median - g/dL (first, third quartile)	10.8 (9.6, 11.1)	9.3 (8.5, 9.8)
Range - g/dL	(9.0, 12.6)	(6.6, 10.6)
Number of units transfused		
n	43	44
Mean - g/dL (standard deviation)	19.2 (8.41)	19.9 (9.28)
Median - g/dL (first, third quartile)	18.0 (12.0, 24.0)	17.0 (13.5, 25.0)
Range - g/dL	(7.0, 36.0)	(7.0, 44.0)
Symptoms associated with transfusion n (%)		
All symptoms	438	426
Change in mental status	14 (3.2)	20 (4.7)
Severe or worsening shortness of breath	69 (15.8)	63 (14.8)
Severe or worsening fatigue	279 (63.7)	264 (62.0)
Other	76 (17.4)	79 (18.5)

Reference: Table 14.1.2.1

In terms of the thrombosis history for patients in the TRIUMPH study, nine patients in the Eculizumab group compared to eight patients in the placebo group had 16 compared to 11 thrombotic events respectively. The history of previous thrombosis between the two treatment arms was similar and is shown in the table below. One patient in the placebo group developed a portal vein thrombosis among all treated patients in the TRIUMPH study.

Table 7. Thrombosis History by Major Adverse Vascular Event (ITT)

Parameter	Eculizumab N = 43		Placebo N = 44	
	Patients n (%)	Events	Patients n (%)	Events
Any thrombosis event	9 (20.9)	16	8 (18.2)	11
Cerebrovascular accident	1 (2.3)	2	0 (0.0)	0
Mesenteric vein thrombosis	0 (0.0)	0	2 (4.5)	2
Other (as reported):				
Ischemic stroke	1 (2.3)	1	0 (0.0)	0
Suspected pulmonary embolus during pregnancy	1 (2.3)	1	0 (0.0)	0
Thrombus	1 (2.3)	1	0 (0.0)	0
Thrombus artery carotis interna left	1 (2.3)	1	0 (0.0)	0
Thrombosis right arm after feeding infusion	1 (2.3)	1	0 (0.0)	0
Pulmonary embolus	1 (2.3)	1	0 (0.0)	0
Thrombophlebitis/deep vein thrombosis	4 (9.3)	5	6 (13.6)	9
Transient ischemic attack	1 (2.3)	3	0 (0.0)	0

Reference: Table 14.1.2.2

The number and type of concomitant medications taken by at least 5% of patients in either treatment group in the ITT population was similar. The sponsor did not formally study drug interactions with Eculizumab during this study or during the clinical development program for Eculizumab. The table below shows the concomitant medication list taken by at least 5% of the patients in either treatment group in the ITT population.

Table 8. Summary of Concomitant Medications Taken by at Least 5% of Patients in Either Treatment Group (ITT)

Anatomical therapeutic chemical classification level 2 term	Eculizumab N = 43 n (%)	Placebo N = 44 n (%)
Vaccines	43 (100)	44 (100)
Antianemic preparations	31 (72.1)	36 (81.8)
Analgesics	30 (69.8)	29 (65.9)
Antithrombotic agents	24 (55.8)	20 (45.5)
Antibacterials for systemic use	23 (53.5)	26 (59.1)
Corticosteroids for systemic use	13 (30.2)	15 (34.1)
Antacids, drugs for treatment of peptic ulcers and flatulence	12 (27.9)	11 (25.0)
Antihistamines for systemic use	9 (20.9)	15 (34.1)
Vitamins	9 (20.9)	8 (18.2)
Psycholeptics	8 (18.6)	9 (20.5)
All other therapeutic products	6 (14.0)	7 (15.9)
Blood substitutes and perfusion solutions	6 (14.0)	4 (9.1)
Psychoanaleptics	6 (14.0)	4 (9.1)
Laxatives	6 (14.0)	6 (13.6)
Mineral supplements	6 (14.0)	8 (18.2)
Antiinflammatory and antirheumatic products	6 (14.0)	10 (22.7)
Beta blocking agents	5 (11.6)	2 (4.5)
Antidiarrheal, intestinal antiinflammatory/antiinfective agents	4 (9.3)	4 (9.1)
Antispasmodics and anticholinergic agents and propulsives	4 (9.3)	4 (9.1)
Sex hormones and modulators of the genital system	4 (9.3)	8 (18.2)
Agents acting on the renin-angiotensin system	4 (9.3)	1 (2.3)
Cough and cold preparations	4 (9.3)	9 (20.5)
Antibiotics and chemotherapy for dermatological use	3 (7.0)	1 (2.3)
Antivirals for systemic use	3 (7.0)	1 (2.3)
Corticosteroids, dermatological preparations	3 (7.0)	1 (2.3)
Nasal preparations	3 (7.0)	2 (4.5)
Diuretics	3 (7.0)	3 (6.8)
Ophthalmologicals	3 (7.0)	3 (6.8)
Calcium channel blockers	2 (4.7)	3 (6.8)
Antiasthmatics	1 (2.3)	3 (6.8)
Drugs for treatment of bone diseases	1 (2.3)	3 (6.8)
Anesthetics	0 (0.0)	5 (11.4)

Reference: Table 14.1.3.1

In the TRIUMPH study, the hemoglobin set point between the two treatment arms was similar and shown in the table below.

Table 9. Summary of Hemoglobin Set Points Established During the Observation Period (ITT)

		Eculizumab N = 43 g/dL	Placebo N = 44 g/dL	*P* Value[a]
Hemoglobin set value				
Mean	(standard deviation)	7.8 (0.79)	7.7 (0.75)	0.7532
Median	(first, third quartile)	7.7 (7.1, 8.5)	7.7 (7.2, 8.3)	
Range		(6.1, 8.8)	(6.2, 9.0)	

Note: The hemoglobin set points for patients were based on transfusion data 12 months prior to Screening.

[a] Wilcoxon's rank sum test was used to calculate the *P* value.

Reference: Table 14.1.1.2

The table below shows the hemoglobin stabilization in the intention to treat population. In the Eculizumab treated group there were 21/43 patients who had hemoglobin stabilization compared to 0/44 patients with hemoglobin stabilization in the placebo group in the TRIUMPH study (P<<0.0001). In the Eculizumab group 22/43 patients did not achieve hemoglobin stabilization. When patients were stratified according to transfusion requirements prior to study entry, (low, intermediate and high strata) there was a statistically significant number of patients who achieve hemoglobin stabilization treated with Eculizumab compared to placebo treated patients. The table below shows the results of the primary endpoint of hemoglobin stabilization in the intention to treat population.

Table 10. Hemoglobin Stabilization (ITT)

Randomization strata	Hemoglobin stabilization?	Eculizumab N = 43 n/N (%)	Placebo N = 44 n/N (%)	*P* Value[a]
Overall (N=87)	Yes	21/43 (48.8)	0/44 (0.0)	0.000000014
	No	22/43 (51.2)	44/44 (100)	
4 to 14 units (n=30)	Yes	12/15 (80.0)	0/15 (0.0)	0.000010521
	No	3/15 (20.0)	15/15 (100)	
15 to 25 units (n=35)	Yes	5/17 (29.4)	0/18 (0.0)	0.019061584
	No	12/17 (70.6)	18/18 (100)	
>25 units (n=22)	Yes	4/11 (36.4)	0/11 (0.0)	0.090225564
	No	7/11 (63.6)	11/11 (100)	

Note: Stabilization was calculated between Baseline and 26 weeks after first dose.

[a] *P* values were calculated using Fisher's exact test.

Reference: Table 14.2.1.1

To assess the robustness of these results a sensitivity analysis was performed based on the rules described previously. This analysis shows of that overall there is a statistically significant level of hemoglobin stabilization in the Eculizumab treated group relative to placebo (P<0.001). These results are shown in the table below.

Table 14.2.1.1.1 Sensitivity Analysis for Hemoglobin Stabilization
Population: ITT

Randomization Strata (a)	Hemoglobin Stabilization	Eculizumab	Placebo	Difference (95% CI)	P Value (b)
Overall (N = 87)	Yes	21/43 (48.8%)	5/44 (11.4%)	0.37 (0.20,0.55)	0.000153935
	No	22/43 (51.2%)	39/44 (88.6%)		
4 - 14 Units (N = 30)	Yes	12/15 (80.0%)	2/15 (13.3%)		0.000678918
	No	3/15 (20.0%)	13/15 (86.7%)		
15 - 25 Units (N = 35)	Yes	5/17 (29.4%)	3/18 (16.7%)		0.443017494
	No	12/17 (70.6%)	15/18 (83.3%)		
> 25 Units (N = 22)	Yes	4/11 (36.4%)	0/11 (0.0%)		0.090225564
	No	7/11 (63.6%)	11/11 (100.0%)		

In the TRIUMPH study, Eculizumab patients required significantly fewer units of packed red blood cells (primary endpoint) during the treatment phase (median 0 units) compared with placebo treated patients (median 10 units) ($P << 0.001$). In addition, there was a statistically significant reduction in the median units of packed red blood cells transfused in each of the three strata subgroups. These results are shown in the table below:

Table 11. Summary of Units Transfused from Baseline to 26 Weeks (ITT)

Randomization strata	Eculizumab	Placebo	*P* value[a]
Overall (N)	43	44	<0.000000001
Mean (standard error)	3.0 (0.67)	11.0 (0.83)	
Median	0.0	10.0	
Range	(0.0, 16.0)	(2.0, 21.0)	
4 - 14 units (n)	15	15	0.000002311
Mean (standard error)	0.4 (0.29)	6.7 (0.72)	
Median	0.0	6.0	
Range	(0.0, 4.0)	(2.0, 12.0)	
15 - 25 units (n)	17	18	0.000665129
Mean (standard error)	4.2 (1.14)	10.8 (1.17)	
Median	2.0	10.0	
Range	(0.0, 15.0)	(2.0, 21.0)	
> 25 units (n)	11	11	0.000301977
Mean (standard error)	4.5 (1.59)	17.0 (1.04)	
Median	3.0	18.0	
Range	(0.0, 16.0)	(10.0, 20.0)	

[a] *P* values were calculated using Wilcoxon's rank sum test.

Reference: Table 14.2.1.2.1

In the TRIUMPH study the secondary analysis of transfusion avoidance showed that overall 22/43 patients in the Eculizumab group compared to 0/44 patients in the placebo group avoided transfusion ($P<<0.001$). The results are shown in the table below.

Table 12. Summary of Patients Who Avoided Transfusions (ITT)

Randomization strata	N	Eculizumab N=43 n/N (%)	Placebo N=44 n/N (%)	*P* value[a]
Overall	87	22/43 (51.2%)	0/44 (0.0%)	0.000000005
4 – 14 units	30	12/15 (80.0%)	0/15 (0.0%)	0.000010521
15 – 25 units	35	6/17 (35.3%)	0/18 (0.0%)	0.007624633
>25 units	22	4/11 (36.4%)	0/11 (0.0%)	0.090225564

Note: Area under the curve was calculated from Baseline to 26 weeks after first dose.

[a] *P* values were calculated using Fisher's exact test.

Reference: Table 14.2.2.1

LDH reflects the degree of intravascular hemolysis. In the TRIUMPH study there was a statistically significant decrease in the LDH AUC for patients treated with Eculizumab compared to placebo both overall and with regard to the randomization strata (P<<0.001). These results are shown in the table below.

Table 13. Area Under the Curve for Lactate Dehydrogenase (U/L × day) (ITT)

Randomization strata	Eculizumab N=43	Placebo N=44	*P* Value[a]
Overall (N)	43	44	<0.000000001
Mean (standard error)	81140.0 (17626.59)	429874.1 (21704.31)	
Median	58586.5	411821.8	
Range	(32417.0, 792005.5)	(161413.5, 886544.0)	
4 - 14 units (n)	15	15	0.000057371
Mean (standard error)	103760.6 (49309.63)	391388.7 (32020.39)	
Median	53609.5	398573.0	
Range	(38340.5, 792005.5)	(230351.5, 697637.5)	
15 - 25 units (n)	17	18	0.000000482
Mean (standard error)	58670.4 (3364.68)	444075.6 (37304.47)	
Median	56126.5	420338.3	
Range	(32417.0, 90114.5)	(161413.5, 886544.0)	
>25 units (n)	11	11	0.000106960
Mean (standard error)	85019.5 (16790.79)	459115.5 (44197.34)	
Median	67181.0	441879.5	
Range	(33230.5, 242071.5)	(234604.5, 711934.0)	

Note: Area under the curve was calculated from Baseline to 26 weeks after first dose.

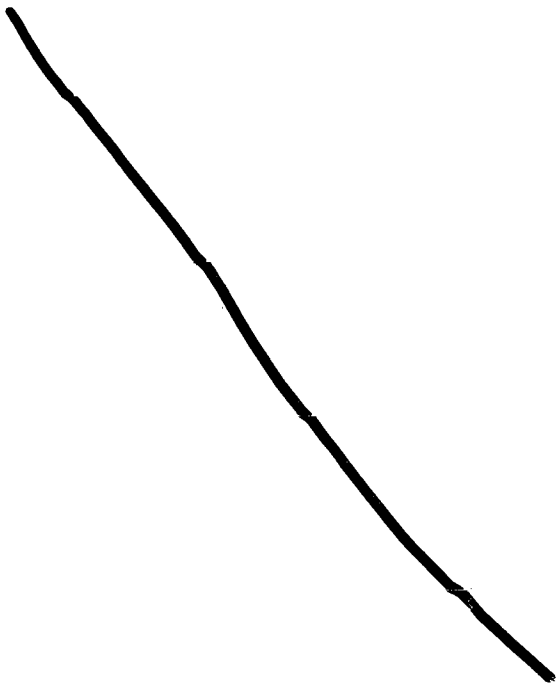
P values were calculated using Wilcoxon's rank sum test.

Reference: Table 14.2.2.2

In order to determine the degree to which Eculizumab impacts the QOL, the sponsor undertook an analysis using the FACIT-F QOL tool. The FACIT-F scale was created to measure the physical symptoms and functional impact of cancer-related fatigue over the past seven days. It was developed using patient and clinician semi-structured interviews to generate items. The FACIT-Fatigue scale summarizes a multidimensional construct in to a single score that combines a fatigue severity/intensity rating with impact assessment. This instrument consists of 13 items - each rated on a 5-point scale from 0="Not at all" to 4="Very much"). The total score has a possible range of 0 to 52. (See Study Endpoints and Label Development (SEALD) review completed January 29, 2007.) In the TRIUMPH study Eculizumab treated patients demonstrated statistically significant improvements in fatigue levels compared to placebo by visit six and at subsequent visits 11, 15 and 18 ($P<0.01$). The results of this analysis are shown in the table below. A sensitivity analysis was performed by the statistics reviewer for the data presented in the table below which showed the finding to be robust (see Statistics review). However, discussions within the Division of Medical Imaging and Hematology Drug Products have revealed that the FACIT-F QOL tool has not been validated for patients in the hematology and oncology setting. Therefore, the results shown in the table below should not be included in labeling for Eculizumab. In addition, the FACIT QOL tool was administered to patients prior to transfusion. No QOL assessment was made after transfusion. Therefore it is unknown how transfusion itself impacted the QOL assessment.

The sponsor undertook an exploratory analysis of QOL using the EORTC QLQ-C30 QOL tool. The EORTC QLQ-C30 was developed to be an "integrated, modular approach for evaluating the quality of life of patients participating in international [oncology] clinical trials." It is comprised of 5 functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status scale, a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and perceived financial impact of the disease. (See SEALD review completed January 29, 2007.) A positive change in global health status and the functional (role, social, cognitive, physical and emotional) course and a negative change in symptom/item (fatigue, pain, dyspnea, appetite loss, insomnia, financial difficulties, constipation, nausea/vomiting and diarrhea) scores indicate improvement. In the TRIUMPH study, Eculizumab treated patients did show improvement in both the functional and symptom/item measures. The results of a QOL analysis using the EORTC QLQ-C30 tool are shown in the table

below. This was an exploratory analysis and this data should not be included in the label for Eculizumab.



In addition, a consult to the Study Endpoints and Label Development (SEALD) was requested on November 1, 2006. This consult evaluated the adequacy of the FACIT-F QOL tool and the EORTC QLQ-C30 QOL tool for use in patients with PNH. The review of the EORTC QLQ-C30 and the FACIT-F tools identified concerns regarding the adequacy of these endpoints to support claims of clinical benefit. With regard to the FACIT-F QOL tool, the consult states that validation experience documents that the scales used by this QOL tool assess distinct components of the QOL construct. However, the review states that it is not clear if the tool measures all of the components of fatigue because fatigue is a multidimensional concept that encompasses both mental and physical attributes. (See SEALD review completed January 29, 2007.) Also, with regard to the EORTC QLQ-C30 QOL tool, the consult states that validation experience documents that the scales assess distinct components of the health-related quality of life construct. However, no evidence is available to support the validity of the instrument to measure the individual domain or individual symptom constructs. (See SEALD review completed January 29, 2007.)

During a teleconference with the sponsor on January 31, 2007 the sponsor was asked to show that the demonstrated improvement in fatigue with Eculizumab did not require improvements in both hemolysis and anemia but was related to either the improvement in hemolysis without

requirement for an improvement in anemia or a drug activity unrelated to the observed drug related improvements in hemolysis or anemia. The sponsor responded to this request, on February 1, 2007, by performing univariate and multiple logistic regression analyses. The sponsor states that in the univariate analysis reductions in intravascular hemolysis and anemia were independently associated with an improvement in fatigue using univariate logistic regression analyses over time. For each reduction by a multiple of the upper limit of the normal range for LDH (223 U/L) the odds ratio was 1.11 (confidence interval of 1.05-1.17) that there would be a four-point or greater improvement in the FACIT-F score ($P<0.001$). For each increase in hemoglobin of 1.0 g/dl, the odds ratio was 1.29 (confidence interval of 1.08-1.53) that there would be a four-point or greater improvement in the FACIT-F score ($P= 0.005$). In the multiple logistic regression analysis reductions in both intravascular hemolysis (reduced LDH) and anemia (increased hemoglobin level) were associated with an improvement in fatigue using multiple logistic regression analysis over time. For each reduction by a multiple of the upper limit of the normal range for LDH (223 U/L), the odds ratio was 1.08 (confidence interval of 1.01-1.14) that there would be a four-point improvement or greater in the FACIT-F score ($P= 0.03$). For each increase in hemoglobin of 1.0 g/dl, the odds ratio was 1.21 (confidence interval of 0.99-1.46) that there would be a four-point or greater improvement in FACIT-F score ($P= 0.058$). The sponsor concludes that the univariate and multivariate logistic regression analyses support that fatigue in patients with PNH is related to intravascular hemolysis. These analyses suggest that Eculizumab may provide an improvement in the QOL of patients with PNH. This conclusion is supported by the statistics review (see Statistics review). However, because a decrease in the degree of hemolysis can impact the severity of anemia it remains that the sponsor has not completely shown that Eculizumab can impact the QOL of patients with PNH independent of its antihemolytic effect and/or its effect on anemia.

In addition, in the TRIUMPH study the sponsor undertook further exploratory analyses of the endpoints of nitric oxide, free hemoglobin measures thrombosis and platelet activity with the essential results as follows:

- Change of the LDH from baseline: reduced LDH from baseline by visit number four $p < 0.001$.
- Platelet activity: 14 North American sites contributed. Activity evaluated by P-selectin and leukocyte platelet aggregation via flow cytometry showed that neither treatment nor time had influence on platelet activity.
- Nitric oxide: consumption favored Eculizumab $p < 0.05$ at visit 12 and $p < 0.01$ at visit 18.
- Free hemoglobin favored Eculizumab by visit 18 the median free hemoglobin was reduced from 40.5mg/dl to 5.2mg/dl $p<0.001$.
- Thrombosis: one patient in the placebo group developed a portal vein thrombosis among all treated patients.

The SHEPHERD study was primarily designed to evaluate the safety of Eculizumab for the treatment of patients with PNH (see section 7 for the review of the safety of Eculizumab demonstrated in the SHEPHERD study). Changes in the conduct of the SHEPHERD study were mainly for clarification of the protocol in terms of laboratory schedule of events and clarification

of site-specific inclusion and exclusion criteria namely, hepatitis and HIV status as required by a German regulatory authorities. Also changes in the protocol included elimination of the upper limit for the number of transfusions required in the inclusion criteria. This change in the protocol does not appear to have impacted the analysis and in fact allowed for patients with greater transfusion needs to be included.

In the SHEPHERD study there were 107 patients screened and nine patients did not meet entry criteria. 98 patients were enrolled into the screening phase. 96 patients completed all visits through visit 17. There was one patient who discontinued the study before visit 17. Patient 102-005 it received five doses of study drug (for induction doses and one maintenance dose) but died approximately 1 month into the study as a result of a cerebral herniation. This patient is described in detail in the Deaths section (7.1.1) of this review.

Protocol deviations included site-specific deviations similar to the TRIUMPH study. Patient protocol deviations were as follows and were minor:

- Patient 018-002 was granted exemption despite a PNH clone < 10%.
- Patient 070-009, 070-012, 070-013 did not have formal PNH diagnoses established at least six months prior to enrollment.
- Patient 015-001 received 600 mg of Eculizumab at visit six instead of 900 mg.
- Seven patients had study medication infused beyond the 14 day treatment phase.

There were six patients (013-001, 013-002, 014-002, 070-006, 091-002, 101-004) that had Eculizumab dosing at a shorter time interval than every 14 days in the SHEPHERD study as is required by the maintenance phase of the dosing regimen. All six of these patients received Eculizumab on day 12 of the maintenance dosing regimen. This was within the parameters of the dosing regimen.

The table below further describes the demographics of the patients included in the SHEPHERD study. The sponsor performed no subgroup analyses based on age, race or gender.

Table 3. Summary of Demographics and Baseline Characteristics (PP)

	Overall N = 97
Gender n (%)	
Male	48 (49.5)
Female	49 (50.5)
Race n (%)	
Caucasian	88 (90.7)
Black	3 (3.1)
Asian	3 (3.1)
Other	3 (3.1)
Age (years)	
Mean (standard deviation)	41.05 (14.41)
Median (first, third quartile)	41.00 (29.00, 51.00)
Range	(18.00, 78.00)
Age groups (years) n (%)	
<65	90 (92.8)
65 to 75	5 (5.2)
≥75	2 (2.1)
Weight (kg)	
n	97
Mean (standard deviation)	73.72 (14.29)
Median (first, third quartile)	73.50 (62.80, 81.10)
Range	(47.63, 120.50)
Height (cm)	
n	96
Mean (standard deviation)	171.70 (10.23)
Median (first, third quartile)	173.00 (163.00, 180.00)
Range	(148.00, 203.00)
Blood Type n (%)	
A-	10 (10.3)
A+	31 (32.0)
B-	3 (3.1)
B+	5 (5.2)
AB-	1 (1.0)
AB+	5 (5.2)
O-	6 (6.2)
O+	36 (37.1)

Reference: Table 14.1.2.1

Generally, patients in the SHEPHERD were of the same median age and had a similar gender distribution to that of the TRIUMPH study. A list of the concomitant medications used by the patients enrolled in the SHEPHERD study is presented below. Of note, 62.9% of patients in this study were on concomitant anticoagulant therapy. Also 47.4% of patients in the SHEPHERD study were on concomitant steroids, and 29.9% had a history of aplastic anemia or myelodysplastic syndrome. The sponsor reported that patients in the SHEPHERD study had an 8.0 U median RBC transfusion requirement in the 12 months prior to enrollment into the study. Also, the mean baseline LDH levels was reported to be 2,051 U/L and the mean free hemoglobin concentration at baseline was reported to be 34.9 g/dl in patients enrolled in the SHEPHERD study.

Table 7. Summary of Concomitant Medications Taken by at Least 5% of Patients (PP)

Anatomical therapeutic chemical classification level 2 term	N = 97 n (%)
Vaccines	97 (100)
Antianemic preparations	84 (86.6)
Analgesics	71 (73.2)
Antithrombotic agents	61 (62.9)
Antibacterials for systemic use	67 (69.1)
Corticosteroids for systemic use	39 (40.2)
Antihistamines for systemic use	32 (33.0)
Antacids, drugs for treatment of peptic ulcers and flatulence	30 (30.9)
Vitamins	24 (24.7)
Mineral supplements	22 (22.7)
Antiinflammatory and antirheumatic products	17 (17.5)
Psycholeptics	19 (19.6%)
Diuretics	16 (16.5)
Sex hormones and modulators of the genital system	13 (13.4)
Psychoanaleptics	13 (13.4)
All other therapeutic products	13 (13.4)
Beta blocking agents	12 (12.4)
Cough and cold preparations	12 (12.4)
Immunosuppressive agents	11 (11.3)
Laxatives	11 (11.3)
Agents acting on the renin-angiotensin system	10 (10.3)
Cardiac therapy	9 (9.3)
Ophthalmologicals	8 (8.2)
Blood substitutes and perfusion solutions	8 (8.2)
Antiemetics and antinauseants	7 (7.2)
Anesthetics	7 (7.2)
Antispasmodics and anticholinergic agents and propulsives	7 (7.2)
Antivirals for systemic use	7 (7.2)
Muscle relaxants	7 (7.2)
Drugs used in diabetes	6 (6.2)
Antiasthmatics	6 (6.2)
Antifungals for dermotological use	6 (6.2)
Antimycotics for systemic use	6 (6.2)
Stomatological preparations	6 (6.2)
Urologicals	6 (6.2)
Antidiarrheal, intestinal antiinflammatory/antiinfective agents	5 (5.2)
Antiepileptics	5 (5.2)
Antibiotics and Chemotherapy for dermotological use	5 (5.2)
Immunostimulants	5 (5.2)
Other nervous system drugs	5 (5.2)

The baseline thrombosis history of patients in the SHEPHERD study is presented in the table below. In the SHEPHERD study 42/97 patients had a history of thrombosis. These 42 patients had a history of 93 thrombotic events.

14.1.2.4 Summary of Thrombosis History by Major Adverse Vascular Event (MAVE)
Population: Per Protocol

	(N = 97)	
Major Adverse Vascular Event	Patient	Event
Any Thrombosis Event	42 (43.3%)	93
Cerebrovascular Accident	10 (10.3%)	11
Mesenteric Vein Thrombosis	5 (5.2%)	5
Portal Vein Thrombosis (Budd-Chiari)	13 (13.4%)	13
Pulmonary Embolus	5 (5.2%)	5
Thrombophlebitis/Deep Vein Thrombosis	17 (17.5%)	26
Transient Ischemic Attack	1 (1.0%)	1
Unstable Angina	1 (1.0%)	1
Other ((post-thrombosis?) portal vein cavernoma)	1 (1.0%)	1
Other (Budd-Chiari syndrome)	1 (1.0%)	1
Other (Deep Vein Thrombosis)	2 (2.1%)	2
Other (Hepatic vein thrombosis)	1 (1.0%)	1
Other (Jugularis interna thrombosis)	1 (1.0%)	1
Other (Recurrent ischemic colitis)	1 (1.0%)	1
Other (Splenic infarct.)	1 (1.0%)	1
Other (Suspected abdominal veins microthrombosis)	1 (1.0%)	1
Other (Thrombophlebitis)	1 (1.0%)	1

NOTE: Major Adverse Vascular Events (MAVEs) were defined in the protocol. Those designated as 'other' were required to have explanatory verbatim terms entered. Patients may have reported more than one MAVEs.

Source Data: 16.2.3.5
Source: \\SAS\Eculizumab\C04-002\Programs\Tables\THROMHXSUM.SAS Run: 05MAY2006 15:19

In the SHEPHERD study the primary endpoint was the LDH AUC. The results of the analysis of the primary endpoint are shown in the table below. There was a significant decrease in the LDH AUC over time in these patients.

Table 9. Area Under the Curve for Lactate Dehydrogenase in U/L over time (PP)

Statistic	Eculizumab N=97	*P* Value[a]
Overall		<0.001
Mean (standard error)	-325375.7 (18296.43)	
Median	-301837.0	
Range	(-881796.5, -39392.5)	

Note: Area under the curve was calculated from Baseline to 26 weeks after first dose.

[a] Based on Wilcoxon signed rank test.

Reference: Table 14.2.1.1

QOL measured by the FACIT-F QOL tool secondary endpoint analysis is shown in the table below. This table shows that fatigue was significantly improved as compared to baseline in these patients (P<0.001).

Table 10. Change of FACIT-Fatigue Scores Between Baseline and All Visits (PP)

	Eculizumab	*P* Value[a]
Baseline		
N	96	
Mean (standard error)	30.8 (1.20)	
Median	33.0	
Range	(5.0,51.0)	
Change from Baseline at:		
Visit 3 (Week 1) (n)	93	<0.001
Mean (standard error)	5.6 (1.00)	
Median	3.0	
Range	(-8.0,40.0)	
Visit 4 (Week 2) (n)	94	<0.001
Mean (standard error)	7.1 (0.98)	
Median	5.0	
Range	(-12.0,34.0)	
Visit 5 (Week 3) (n)	95	<0.001
Mean (standard error)	9.1 (1.10)	
Median	7.0	
Range	(-22.0,44.0)	
Visit 6 (Week 4) (n)	93	<0.001
Mean (standard error)	8.9 (1.12)	
Median	8.0	
Range	(-18.0,37.0)	
Visit 10 (Week 12) (n)	90	<0.001
Mean (standard error)	9.9 (1.20)	
Median	7.5	
Range	(-13.0,43.0)	
Visit 14 (Week 20) (n)	90	<0.001
Mean (standard error)	11.6 (1.25)	
Median	9.5	
Range	(-18.0,42.0)	
Visit 17 (Week 26) (n)	94	<0.001
Mean (standard error)	11.8 (1.20)	
Median	8.5	
Range	(-10.7,44.0)	

[a] Based on Wilcoxon signed rank test.
Reference: Table 14.2.2.1.2

As in the TRIUMPH study analyses of QOL, on January 31, 2007, the sponsor was asked to show that improvement in fatigue with Eculizumab did not require improvements in both hemolysis and anemia but was related to either the improvement in hemolysis without requirement for an improvement in anemia or a drug activity unrelated to the observed drug-related improvements in hemolysis or anemia. The sponsor responded on February 1, 2007, stating that Eculizumab treatment resulted in significant improvements in fatigue and hemolysis without meaningful changes in transfusion requirements in the SHEPHERD study population. The sponsor stated that statistically significant improvements in fatigue were observed in the < 4 U/year pretreatment transfusion stratum. The sponsor indicated that this improvement in fatigue was obtained in patients with minimal pretreatment transfusion requirements and without demonstrable reductions in their transfusion requirements with Eculizumab treatment. The

sponsor indicated that the baseline fatigue score for these patients (n=21) was 27.6. The mean change from baseline fatigue score at week 26 for these patients was 13.1 (P<0.001). In this group of 21 patients a median of 0.0 units of red blood cells were transfused during the 26 weeks pretreatment and a median of 0.0 units of packed red blood cells were transfused during the 26 weeks of treatment. The analysis performed by the sponsor appears to support the claim that Eculizumab may improve the QOL of patients with PNH regardless of Eculizumab's affect on hemolysis or anemia. However, the SHEPHERD study was an uncontrolled and open label study and it is not clear what the effect of placebo may have been or if there may have been biased patient reporting in favor of improved QOL.

In the SHEPHERD study two patients developed thrombotic events (one patient with deep vein thrombosis and one patient with pulmonary embolism). The event rate was low however, a majority of patients were on concomitant anticoagulant treatment and there was no comparator arm in this trial. These issues confound the conclusion regarding the effect of Eculizumab on the rate of thrombosis.

Table 14.2.3.3 Summary of Thrombosis Events
Population: Per Protocol

Major Adverse Vascular Event	(N = 97)
Any Thrombosis Event	2 (2.1%)
Other (Deep Vein Thrombosis)	1 (1.0%)
Pulmonary Embolus	1 (1.0%)

The baseline transfusion history of the patients enrolled in the SHEPHERD study is shown in the table below. Patients had a median hemoglobin of 7.5 g/dl and a median transfusion requirement of eight units of red blood cells over two years. The sponsor reports that shortness of breath and fatigue was the two most common reported symptoms which triggered transfusion.

Table 5. Transfusion History (PP)

Parameter	Eculizumab N = 97
Hemoglobin prior to transfusion	
n	94
Mean - g/dL (standard error)	7.7 (0.13)
Median - g/dL (first, third quartile)	7.5 (6.9, 8.3)
Range - g/dL	(4.5, 12.4)
Hemoglobin after transfusion	
n	42
Mean - g/dL (standard deviation)	9.4 (0.22)
Median - g/dL (first, third quartile)	9.4 (8.2, 10.1)
Range - g/dL	(6.3, 13.2)
Number of units transfused	
n	97
Total units transfused	1546
Mean (standard error)	15.9 (1.67)
Median (first, third quartile)	8.0 (4.0, 24.0)
Range	(0.0, 66.0)
Symptoms associated with transfusion	
All symptoms	728
Angina	1 (<1%)
Change in mental status	5 (1%)
Severe or worsening shortness of breath	143 (20%)
Severe or worsening fatigue	448 (62%)
Other	131 (18%)

Reference: Table 14.1.2.3

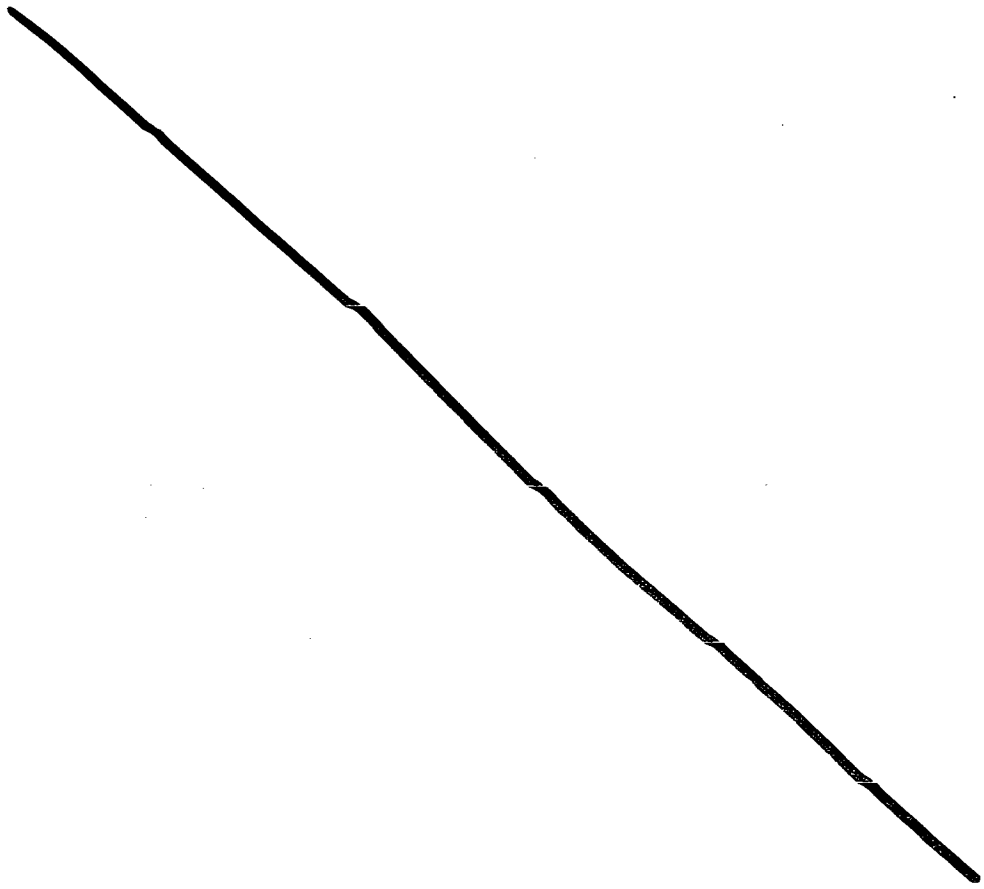
The sponsor undertook an analysis of the number of units of packed red blood cells transfused and transfusion avoidance and the analyses are shown in the table below. The results shown here for the SHEPHERD study for these analyses are compared to baseline. In addition, LDH levels (secondary endpoint) and free hemoglobin analyses (exploratory endpoint) are shown in the table below. This table shows that compared to baseline in the SHEPHERD study patients had improved transfusion avoidance has no packed red blood cell units were transfused. In addition, LDH levels decreased compared to baseline. Also, free hemoglobin levels decreased compared to baseline.

	TRIUMPH			**SHEPHERD**	
	Placebo N = 44	Ecu N = 43	P – Value1	Ecu N = 97	P – Value2
Stabilization of hemoglobin levels (%)	**0.0**	**48.83**	**< 0.001**	N/A	N/A
Median PRBC Units Transfused/patient	**10.0**	**0.03**	**< 0.001**	0.0	< 0.001
Transfusion Avoidance (%)	0.0	51.2	< 0.001	55.7	< 0.001
LDH levels at 26 wks	2,166.5	239.0	< 0.001	270.0	< 0.001
Free Hb at 26 weeks	61.6	5.2	< 0.001	6.0	< 0.001

In the SHEPHERD study six patients had Eculizumab dosing during the maintenance phase given more frequently then every 14 days. These patients were still treated according to the protocol specified dosing regimen of 14 +/- 2 days. The mean number of doses of Eculizumab administered to these six patients was 29.5 (range 29-31 doses). The table below shows the number of doses at each of the intervals and the change from baseline in LDH and hemoglobin for these six patients. At the dosing interval of every 14 days these six patients had a mean decrease in hemoglobin of 0.44 mg/dl. Administration of Eculizumab more frequently caused an increase in hemoglobin and further decrease in LDH as is shown in the table below. In an e-mail communication on February 21, 2007 the sponsor reported that only these 6/196 PNH patients have been treated more frequently then the maintenance specified dosing interval of every 14 days.

Parameter	Dosing Interval		
	Every 12 days	Every 13 days	Every 14 Days
Number of doses	71	45	25
Mean change LDH (U/L) from baseline	-1998	-2519	-755
Mean change hemoglobin (mg/dl) from baseline	1.26	1.44	-0.44

An additional exploratory analysis was conducted on QOL using the EORTC QLQ-C30 tool. A positive change in global health status and functional scores (role, social, cognitive, physical, emotional) and eight negative change in symptom/item scores (fatigue, pain, dyspnea, appetite loss, insomnia, financial difficulties, constipation, nausea/vomiting and diarrhea) would indicate an improvement. Changes in this QOL tool's scores from baseline were analyzed using a mixed-effects model with baseline as a covariate, time as fixed effect and patient as a random effect. The sponsor indicates that there was a statistically significant improvement seen for overall visits in 13/15 items including: global health status, role, social, cognitive, physical, emotional, fatigue, pain, dyspnea, appetite loss, insomnia, nausea/vomiting and diarrhea symptom domains. The table below shows these results.



6.1.5 Clinical Microbiology

Not Applicable

6.1.6 Efficacy Conclusions

The TRIUMPH study was a randomized, double-blind, placebo-controlled, multicenter study of Eculizumab or placebo administered by IV infusion to 87 patients with hemolytic transfusion dependent PNH patients. The treatment arms were similar in terms of patient demographics, thrombosis and transfusion history. In this study hemoglobin stabilization (a co primary endpoint) was achieved in 48.8% of Eculizumab treated patients indicating that these patients did not require any transfusions during the 26 week study duration because their hemoglobin levels remained above their individual set points. Hemoglobin stabilization did not occur among any of the placebo patients and the difference between the treatment groups was statistically significant. A sensitivity analysis performed on the hemoglobin stabilization endpoints confirmed this efficacy outcome. After treatment with Eculizumab, statistically significant differences in hemoglobin stabilization were observed in the low and middle transfusion strata but not the high

strata. In addition a statistically significant reduction in the number of packed red blood cell units transfused (a co-primary endpoint) was achieved in the Eculizumab group compared with placebo. During the 26 week study the median units transfused per patient was 0.0 in the Eculizumab group and 10.0 in the placebo group regardless of transfusion strata.

Secondary endpoint analyses for efficacy showed transfusion avoidance was achieved in 22/43 Eculizumab patients and in no placebo patients which was statistically significant. Secondary endpoint analysis showed a statistically significant overall improvement in LDH AUC. Also, there was a statistically significant improvement in LDH AUC in each transfusion stratum after treatment with Eculizumab compared to the placebo. The sponsor analyzed the QOL in this study using the FACIT-Fatigue QOL tool. Eculizumab treated patients had a similar mean number of QOL assessments per patient compared to placebo treated patients in the TRIUMPH study (8.7 (range 5-9) assessments, n = 43 Eculizumab treated patients compared to 8.6 (range 3-9) assessments, n = 44 placebo treated patients). Eculizumab treated patients demonstrated statistically significant improvements in fatigue levels compared to placebo treated patients by visit six and at subsequent visits. A sensitivity analysis was performed by the statistics reviewer for the data presented in the table below which showed the finding to be robust (see Statistics review). However, because the QOL tool was administered to patients prior to transfusion without a follow-up QOL tool administration immediately after transfusion, is difficult to ascertain Eculizumab's effect on QOL independent of transfusion. The sponsor was asked to demonstrate that improvement in fatigue with Eculizumab did not require improvements in both hemolysis and anemia but was related to either the improvement in hemolysis without requirement for an improvement in anemia or a drug activity unrelated to the observed drug related improvements in hemolysis or anemia. However, the sponsor was not able to demonstrate that improvement in fatigue with Eculizumab did not require improvements in both hemolysis and anemia but was related to either the improvement in hemolysis without requirement for an improvement in anemia or a drug activity unrelated to the observed drug related improvements in hemolysis or anemia due to the fact that the sponsor did not assess the effect of red blood cell transfusion by itself on QOL.

The sponsor performed a series of exploratory endpoint analyses including comparison of change of lactate dehydrogenase from baseline, an analysis of QOL using the EORTC QLQ-C30 tool, platelet activity, nitric oxide measure, free hemoglobin measurements and thrombosis. In the TRIUMPH study, Eculizumab treated patients did show improvement in both the functional and symptom/item measures when assessed using the EORTC QLQ-C30 tool and fatigue using the FACIT-F tool. The QOL analyses suggest that Eculizumab may provide an improvement in the QOL of patients with PNH. This conclusion is supported by the statistics review (see Statistics review). However, because a decrease in the degree of hemolysis can impact the severity of anemia it remains that the sponsor has not completely shown that Eculizumab can impact the QOL of patients with PNH independent of its antihemolytic effect and/or its effect on anemia.

The review of the EORTC QLQ-C30 and the FACIT-F tools by the SEALD team identified concerns regarding the adequacy of these endpoints to support claims of clinical benefit. With regard to the FACIT-F QOL tool, the review states that validation experience documents that the scales used by this QOL tool assess distinct components of the QOL construct. However, the review further states that it is not clear if the tool measures all of the components of fatigue

because fatigue is a multidimensional concept that encompasses both mental and physical attributes. (See SEALD review completed January 29, 2007.) Also, with regard to the EORTC QLQ-C30 QOL tool, the review states that validation experience documents that the scales assess distinct components of the health-related quality of life construct. However, the review further states that no evidence is available to support the validity of the instrument to measure the individual domain or individual symptom constructs. (See SEALD review completed January 29, 2007.)

Nitric oxide measures and free hemoglobin measures favored the Eculizumab treated patients. The exploratory analysis for platelet activity by visit showed that there is no statistically significant change from baseline between the treatment groups. However, analyses of the effect of Eculizumab on the incidence of thrombosis are confounded by the fact that approximately 50% of patients in the Eculizumab treatment arm were on concomitant anticoagulant therapy.

Therefore it appears that Eculizumab is effective in stabilizing hemoglobin and decreasing the number of packed red blood cell transfusions required in transfusion dependent PNH patients. Secondary endpoint analyses for transfusion avoidance and LDH AUC provide additional support that Eculizumab is effective in the treatment of PNH. However, QOL measures using the FACIT- F tool and EORTC QLQ-C30 tool are confounded by the fact that no assessment of effect of transfusion on QOL was performed. Furthermore, with regard to the FACIT-F tool it is not clear if the tool measures all of the components of fatigue because fatigue is a multidimensional concept that encompasses both mental and physical attributes. With regard to the EORTC QLQ-C30 tool there is no evidence available to support the validity of the instrument to measure the individual domain or individual symptom constructs. Analyses of the effect of Eculizumab on the incidence of thrombosis are confounded by the fact that approximately 50% of patients in the Eculizumab treatment arm were on concomitant anticoagulant therapy.

In the open label SHEPHERD study, which was designed primarily to assess the safety of Eculizumab treatment in patients with PNH, Eculizumab decreased the LDH AUC compared to baseline and may improve quality of life as measured by the FACIT-F QOL instrument. Eculizumab treatment resulted in significant improvements in fatigue and hemolysis without meaningful changes in transfusion requirements in the SHEPHERD study population. The sponsor stated that statistically significant improvements in fatigue were observed in the < 4 U/year pretreatment transfusion stratum. The sponsor indicated that this improvement in fatigue was obtained in patients with minimal pretreatment transfusion requirements and without demonstrable reductions in their transfusion requirements with Eculizumab treatment. The sponsor indicated that the baseline fatigue score for these patients (n=21) was 27.6. The mean change from baseline fatigue score at week 26 for these patients was 13.1 ($P<0.001$). In this group of 21 patients a median of 0.0 units of red blood cells were transfused during the 26 weeks pretreatment and a median of 0.0 units of packed red blood cells were transfused during the 26 weeks of treatment. Clinically, FACIT-F scores generally ≤ 30 are considered to be related to difficulty performing everyday activities. Patients with scores above 30 can generally perform activities of daily living.[3] In addition, the SHEPHERD study was able to show that Eculizumab can decrease transfusion requirements and free hemoglobin levels. Using the EORTC QLQ-C30 QOL tool, in an exploratory analysis, the sponsor was able to show that in patients treated with

Eculizumab there were improvements in 13/15 measures including: global health status, role, social, cognitive, physical, emotional, fatigue, pain, dyspnea, appetite loss, insomnia, nausea/vomiting and diarrhea symptom domains.

Conclusions regarding the effect of Eculizumab on thrombosis are confounded because of the fact that a majority of patients (59/97) were on concomitant anticoagulant therapy in the SHEPHERD. With regard to the FACIT-F tool it is not clear if the tool measures all of the components of fatigue because fatigue is a multidimensional concept that encompasses both mental and physical attributes. With regard to the EORTC QLQ-C30 QOL tool, no evidence is available to support the validity of the instrument to measure the individual domain or individual symptom constructs. (See SEALD review completed January 29, 2007.)

Therefore, it appears that Eculizumab is effective in the treatment of patients with transfusion dependent PNH by decreasing hemolysis which results in a stabilization of hemoglobin levels and avoidance of transfusion. It also appears that Eculizumab may improve QOL in patients with PNH in terms of decreasing fatigue and by improving other QOL parameters. Due to the fact that a large number of patients were on concomitant anticoagulant therapy a conclusion regarding Eculizumab's effect on thrombosis incidence rates cannot be made.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In the TRIUMPH study safety was assessed by examination of treatment emergent adverse events, clinical laboratory results, electrocardiogram data and vital sign measurements collected during the treatment phase and the post-treatment phase. All treatment emergent adverse events were presented by the sponsor using descriptive statistics. The Fisher exact test was used to compare the differences in treatment emergent adverse events between the treatment groups. In addition, laboratory data was analyzed using descriptive statistics.

In the TRIUMPH study the extent of study drug exposure in the ITT population is shown in the table below. The duration of months (median 6.1 months for both Eculizumab and placebo treated patients) on study drug and the number of study drug infusions (median 16.0 infusions for both Eculizumab and placebo treated patients) was similar between the two treatment arms.

Table 16. Extent of Study Drug Exposure (ITT)

	Eculizumab N = 43	Placebo N = 44
Duration (months) on study drug[a]		
Mean (standard deviation)	6.0 (0.85)	5.2 (1.81)
Median (1st and 3rd quartiles)	6.1 (6.1, 6.1)	6.1 (6.0, 6.1)
Range	1.9, 7.1	0.9, 6.4
Number of study drug infusions		
Mean (standard deviation)	15.9 (1.90)	14.3 (3.77)
Median (1st and 3rd quartiles)	16.0 (16.0, 16.0)	16.0 (16.0, 16.0)
Range	7.0, 19.0	5.0, 17.0
Total amount (mg) of eculizumab infused[b]		
Mean (standard deviation)	13032.3 (1680.95)	not applicable
Median (1st and 3rd quartiles)	13200.0 (13200.0, 13200.0)	not applicable
Range	5100.0, 15900.0	not applicable

[a] Duration = (last dose date – first dose date + 1)/30.

[b] Total amount = 5 * total volume infused

Reference: Table 14.1.3.2

In the SHEPHERD study the extent of drug exposure is shown in the table below. The median number of months on treatment was 6.1 and the median number of drug infusions was 16.

Table 12. Extent of Study Drug Exposure (PP)

	Eculizumab N = 97
Duration (months) on study drug[a]	
Mean (standard deviation)	6.0 (0.53)
Median (1st and 3rd quartiles)	6.1 (6.0, 6.1)
Range	1.0, 6.1
Number of study drug infusions	
Mean (standard deviation)	15.8 (1.19)
Median (1st and 3rd quartiles)	16.0 (16.0, 16.0)
Range	5.0, 17.0
Total amount (mg) of eculizumab infused	
Mean (standard deviation)	12950.5 (1099.37)
Median (1st and 3rd quartiles)	13200.0 (13200.0, 13200.0)
Range	3300.0, 14100.0

[a] Duration = (last dose date – first dose date + 1)/30.

Reference: Table 14.1.3.2

7.1.1 Deaths

In the TRIUMPH study no deaths occurred.

Otherwise there were a total of 7 depth deaths in all of the Eculizumab studies combined. There were three deaths in non-PNH studies and four deaths in PNH studies. The narratives for these patients are as follows:

- C99-004 non-PNH Eculizumab treated patient death: this patient was a 37-year-old black male with a history of idiopathic membranous glomerulonephropathy. This patient died due to [redacted]
- E 99-001 non- PNH Eculizumab treated patient death: this patient was a 61-year-old Hispanic female with a history of rheumatoid arthritis. She had been on eight months of Eculizumab treatment in study E 99-001. The patient presented with chest pain and developed fever or chills and a blood culture positive for Klebsiella. The patient was given antibiotics and underwent a laparoscopic cholecystectomy to remove a common bile duct stone. The patient had postoperative complications related to an intra-abdominal abscess. Four weeks after the admission the patient had a further complication with a perforated sigmoid colon which again required antibiotic treatment. However, two weeks after the sigmoid resection the patient developed Candida sepsis and ventricular tachycardia and died. It was considered buying be investigator that his death was unrelated to study medication.
- C 01-004 non--PNH treated with placebo death: this patient was a 55-year-old black woman with a history of rheumatoid arthritis. Two months after the patient was given placebo she developed an incarcerated right inguinal hernia and acute bowel obstruction. She required intensive management with ventilator support and aggressive fluid management due to postoperative sepsis. Three weeks postoperatively she developed acute respiratory distress. The patient subsequently had a myocardial infarction and a presumed pulmonary embolism and died.
- C 04-002 PNH Eculizumab treated patient death: this patient was a 31 year-old Caucasian male with a history of PNH. The patient was admitted to hospital with low back pain and pneumonia two weeks after his last dose of study medication. The patient had been on treatment 11 months prior to the admission. A diagnosis of pulmonary embolism was made based on CT scan; however, the patient refused full anticoagulation due to fear of bleeding. The patient's low back pain was diagnosed as a disc prolapse. He had in underlying history of aplastic anemia which required cyclosporine treatment. While in hospital he developed acute renal failure and was treated with intravenous fluids. The patient had respiratory failure 10 days after admission and was declared brain-dead on day 14 after admission due to cerebral herniation secondary to a cerebral hemorrhage. During his hospitalization it was noted that the patient had LDH levels below his pretreatment levels and the primary investigator observed no serious hemolysis otherwise.
- E 05-001 PNH Eculizumab treated patient death: this patient was a 71 year-old Caucasian male with a history of PNH and myelodysplastic syndrome. During the study the patient developed cellulitis, sepsis and acute renal failure subsequent to a [redacted]

The patient was hospitalized and subsequently developed a viral infection. In addition the patient was on prednisone and solucortef during the hospitalization. The patient was admitted to hospital with increasing fatigue and lower extremity petechiea and thrombocytopenia. He was diagnosed with progression of his myelodysplastic syndrome to chronic myelomonocytic leukemia. The patient subsequently died due to his underlying disease.

- E 05-001 PNH Eculizumab treated patient death: this patient was a 63-year-old Caucasian female who is enrolled initially in the TRIUMPH study. Subsequently the patient was enrolled in the extension study E 05-001. The patient had a significant past medical history for adenocarcinoma of the stomach which was not completely resected. The patient's treatment with Eculizumab was essentially unremarkable with stabilization of her hemoglobin. Eight months after starting treatment in the extension study, an ultrasound of the patient's abdomen and subsequent CT scan showed multiple lesions in the liver. Ultrasonography showed an enlarged with lymph node in the liver hilus along with mediastinal lymphadenopathy and intrapulmonary lesions. In addition, a paravertebral mass was recognized. The patient underwent ultrasound guided biopsy of the liver lesions which demonstrated metastasis of the adenocarcinoma. The patient was enrolled in the extension study for a full year and received treatment with Eculizumab throughout. The patient died approximately 13 months after having started the extension study due to progression of her underlying adenocarcinoma.
- Physician sponsored PNH Eculizumab treated study patient death: this patient was a 60 year old patient with a history of PNH for 10 years. The patient was [redacted] The patient had undergone 10 months of treatment with Eculizumab. She presented with jaundice, gallstones and bacteremia. The patient was treated with a biliary drain because she was a poor surgical candidate. She progressed with one month of intermittent acute cholecystitis and presumed sepsis while off Eculizumab treatment. The patient had progressive decrease in her hemoglobin to a level of 2.0 g/dl and died due to a presumed anoxic cerebrovascular event. The physician considered the patient's death unlikely to be related to Eculizumab treatment.

Review of the narratives for these cases as well as the case report forms indicates that it is unlikely that Eculizumab was directly related to these patient deaths.

7.1.2 Other Serious Adverse Events

The table below shows the serious adverse events that occurred in the TRIUMPH study. In this study 4/43 patients in the Eculizumab group compared to 9/44 patients in the placebo group had serious adverse events. The most prevalent serious adverse event was exacerbation of PNH which occurred and one Eculizumab treated patient and three placebo treated patients. In addition, overall one Eculizumab treated patient reported one serious adverse event associated with infection compared to four placebo patients who reported six infections related adverse events.

Table 21. Treatment-emergent Serious Adverse Events by Severity (Safety)

	Eculizumab N=43			Placebo N=44		
	Mod n	Sev n	Total n (%)	Mod n	Sev n	Total n (%)
Total number of events	3	1	4	7	9	16
Number of patients reporting SAEs	3	1	4 (9.3)	3	6	9 (20.5)
System organ class (presents total number of patients reporting at least 1SAE) Preferred term (presents total number of events reported)						
Blood and lymphatic system disorders	**0**	**1**	**1 (2.3)**	2	5	7 (15.9)
Anaemia	0	0	0 (0.0)	0	1	1 (2.3)
Haemolysis	0	0	0 (0.0)	1	0	1 (2.3)
Neutropenia	0	0	0 (0.0)	0	2	2 (4.5)
Paroxysmal nocturnal haemoglobinuria	0	1	1 (2.3)	1	2	3 (6.8)
General disorders and administration site conditions	**0**	**0**	**0 (0.0)**	**1**	**0**	**1 (2.3)**
Pyrexia	0	0	0 (0.0)	1	0	1 (2.3)
Infections and infestations	**1**	**0**	**1 (2.3)**	**2**	**2**	**4 (9.1)**
Cellulitis	0	0	0 (0.0)	0	1	1 (2.3)
Central line infection	0	0	0 (0.0)	1	0	1 (2.3)
Folliculitis	0	0	0 (0.0)	0	1	1 (2.3)
Streptococcal bacteraemia	1	0	1 (2.3)	0	0	0 (0.0)
Upper respiratory tract infection	0	0	0 (0.0)	1	0	1 (2.3)
Urinary tract infection	0	0	0 (0.0)	1	0	1 (2.3)
Viral infection	0	0	0 (0.0)	0	1	1 (2.3)
Musculoskeletal and connective tissue disorders	**1**	**0**	**1 (2.3)**	**0**	**0**	**0 (0.0)**
Intervertebral disc protrusion	1	0	1 (2.3)	0	0	0 (0.0)
Renal and urinary disorders	**1**	**0**	**1 (2.3)**	**0**	**0**	**0 (0.0)**
Renal colic	1	0	1 (2.3)	0	0	0 (0.0)

Mod = Moderate Sev = Severe

Only the most severe of the adverse events for each patient within each system organ class/preferred term was counted.

Mild SAEs were reported, but only moderate and severe SAEs are summarized in this table.

Reference: Table 14.3.1.4.2

There were three patients who developed meningococcal infection while enrolled in the Eculizumab trials. The narratives for these cases are as follows:

- Meningococcal infection in a vaccinated PNH patient: the patient is a 24-year-old male with a past medical history notable for PNH who had received approximately 12 months of Eculizumab in the E05-001 study after receiving placebo in the C04-001 study. His last dose of Eculizumab was three days prior to the event. The patient was well in the morning but began feeling ill over the course of the day. On presentation the patient had a systolic blood pressure of 90 mmHg and a temperature of 104°F. He underwent a lumbar puncture which was normal and laboratories showed him to have a hemoglobin of 10 g/dl and an LDH of 211 IU/L. The patient was placed on vasopressors and antibiotics and given intravenous fluids. The patient developed hemolysis as evidenced by dark urine and a drop in his hemoglobin to a level of 6.3 g/dl. A blood culture was positive for *Neisseria meningitidis*. The patient was discharged home with antibiotics four days after

admission. The patient was reported to be doing well with no hemolysis or other PNH complications noted.

- Meningococcal infection in a vaccinated PNH patient: the patient is a 54 year-old female who participated initially in the SHEPHERD study and then was enrolled in the extension study E05-001. The patient had been on Eculizumab for a period of approximately 14 months. The patient presented with a fever, cough, mild frontal headache and vomiting. The patient was hypotensive, tachycardic and febrile. She was given intravenous fluids and antibiotics intravenously at the time of her presentation. The patient's urine was positive for dark blood. Her LDH was reported to be 1242 U/L and her hemoglobin was 67 g/dl. Blood cultures were positive for *Neisseria meningitidis*. The patient was discharged home with a five-day course of oral antibiotics. The patient's LDH at the time of discharge and at one month follow-up was in the 2000-3000 range.
- Meningococcal infection in an unvaccinated non-PNH patient: this patient is a 22 year-old female with a history of idiopathic membranous glomerulonephritis. She was not vaccinated against meningococcal disease. She had been on Eculizumab treatment 8 mg/kg every two weeks for a total of seven months when she developed a one-day history of nausea, vomiting, abdominal pain and body aches. The patient presented with a tachycardia and tachypnea along with a temperature of 104° F. The patient was orthostatic and had a serum creatinine of 2.6 mg/dl (baseline 0.7 mg/dl). The patient had a lumbar puncture which was positive for *Neisseria meningitidis*. The patient was noted to have gangrene in some of her digits requiring partial amputation of several distal hand digits. In addition the patient's course was complicated by pneumonia and a probable pulmonary embolism. The patient was discharged to a rehabilitation facility after surgery and prolonged antibiotic treatment.

The incidence of herpes simplex infection appeared increased in patients treated with Eculizumab in PNH studies. In the TRIUMPH and SHEPHERD studies 8/140 patients developed herpes simplex infection. These infections were mild or moderate in severity in all patients. In 2/8 of the patients it was felt that Eculizumab was possibly related to this adverse event. The sponsor notes that these patients had increased risk factors for developing herpes simplex infection such as:

- Previous herpes infection in four patients.
- Previous aplastic anemia in two patients.
- History of other viral (CMV) reactivation in one patient.
- A history of sickle cell disease and one patient.

The sponsor notes that in the general population the prevalence of herpes simplex is reported to be approximately 68%.[4]

In the SHEPHERD study, 12/97 patients were reported to have serious adverse events. The most common serious adverse event was anemia which was moderate reported in three patients. The table below shows the serious adverse event rates for the SHEPHERD study. There was one patient in this study who died (number 102-005) and is described in section 7.1 .1 of this review.

Table 17. Treatment-Emergent Serious Adverse Events by Severity (Safety)

	Eculizumab			
	Mild n	Moderate n	Severe n	Total n (%)
Total number of events	0	13	11	24
Number of patients reporting SAEs		4	8	12 (12.4)
Blood and lymphatic system disorders	0	5	0	5 (5.2)
Anaemia	0	3	0	3 (3.1)
Anaemia macrocytic	0	1	0	1 (1.0)
Haemolysis	0	1	0	1 (1.0)
Thrombocytopenia	0	1	0	1 (1.0)
Gastrointestinal disorders	0	1	0	1 (1.0)
Abdominal pain	0	1	0	1 (1.0)
General disorders and administration site conditions	0	1	0	1 (1.0)
Pyrexia	0	1	0	1 (1.0)
Hepatobiliary disorders	0	0	1	1 (1.0)
Cholecystitis	0	0	1	1 (1.0)
Infections and infestations	0	1	0	1 (1.0)
Pyelonephritis	0	1	0	1 (1.0)
Injury, poisoning and procedural complications	0	1	1	2 (2.1)
Brain herniation	0	0	1	1 (1.0)
Rib fracture	0	1	0	1 (1.0)
Metabolism and nutrition disorders	0	1	0	1 (1.0)
Hypokalaemia	0	1	0	1 (1.0)
Musculoskeletal and connective tissue disorders	0	0	1	1 (1.0)
Intervertebral disc protrusion	0	0	1	1 (1.0)
Nervous system disorders	0	1	4	5 (5.2)
Convulsion	0	0	1	1 (1.0)
Epilepsy	0	0	1	1 (1.0)
Haemorrhagic cerebral infarction	0	0	1	1 (1.0)
Headache	0	1	1	2 (2.1)
Psychiatric disorders	0	0	1	1 (1.0)
Anxiety	0	0	1	1 (1.0)
Renal and urinary disorders	0	1	2	3 (3.1)
Nephrolithiasis	0	0	1	1 (1.0)
Renal impairment	0	0	1	1 (1.0)
Renal insufficiency	0	1	0	1 (1.0)
Vascular disorders	0	0	1	1 (1.0)
Thromboembolism	0	0	1	1 (1.0)

N=97
Reference: Table 14.3.1.4.2

7.1.3 Dropouts and Other Significant Adverse Events

In the TRIUMPH study the following patients were discontinued from the study:

- Patient 170-001 (Eculizumab) discontinued due to difficulty with travel requirement.

- Patient 028-003 (Eculizumab) was discontinued when it was discovered she was pregnant.

There was one patient who dropped out due to adverse events in the SHEPHERD study. This patient (number 102-005) is described in section 7.1.1 this review.

7.1.3.1 Overall profile of dropouts

The frequency of any discontinuation due to adverse event treatment was similar in the Eculizumab and placebo treated populations in the TRIUMPH study (Eculizumab-2.3%, placebo-0.0%) and in the uncontrolled studies in patients with PNH. The single discontinuation due to adverse event in the TRIUMPH study was a patient treated with Eculizumab who subsequently became pregnant. In the uncontrolled PNH studies there were no discontinuations due to adverse events reported in 193 patients prior to database lock. However it became known that a single patient in the extension study E05-001 withdrew from the study due to a serious adverse event which was determined to be progression of his pre-existing myelodysplastic syndrome to chronic myelomonocytic leukemia and which was considered to be unrelated to study medication. The patient subsequently died due to his pre-existing condition. A second patient discontinued from the uncontrolled study due to a newly diagnosed myelodysplastic syndrome. The patient was withdrawn to prepare for a possible bone marrow transplantation. The cause of the MDS was considered to be the patient's underlying PNH. Discontinuation of Eculizumab treatment or noncompliance with Eculizumab treatment was not associated with subsequent serious hemolysis in the TRIUMPH or SHEPHERD PNH studies. Five patients who discontinued Eculizumab treatment after receiving Eculizumab for a range of 29-715 days prior to withdrawal showed no evidence of serious hemolysis following discontinuation of Eculizumab. In addition, nine patients with 12 episodes of noncompliance with the dosing regimen of Eculizumab showed no episodes in which hemolysis was increased over pretreatment levels. Therefore, it appears that he discontinuation due to adverse events was low in frequency in both the controlled and uncontrolled PNH studies.

Thus far in the SHEPHERD study there was one patient who dropped out due to death (number 102-005). This patient is described in section 7.1 .1 of this review.

7.1.3.2 Adverse events associated with dropouts

The frequency other any adverse event leading to discontinuation was generally similar in the Eculizumab and placebo treated populations in the TRIUMPH study (Eculizumab 2.3% compared to placebo 0.0%) and the uncontrolled PNH studies (Eculizumab 0.0%) as well as the placebo-controlled non-PNH studies (Eculizumab 6.5% compared to placebo 6.8%) and the uncontrolled non-PNH studies (Eculizumab 8.3%). The treatment emergent adverse events leading to premature discontinuation by system organ class and preferred term occurring throughout the PNH studies include:

- Pregnancy 1/43 patients in the TRIUMPH study in the Eculizumab group and 1/458 in the non-PNH uncontrolled study.

- Respiratory, thoracic and mediastinal disorders in the non-PNH placebo-controlled study (5/526 patients in the Eculizumab group) and 2/458 patients in the non-PNH uncontrolled studies.
- Infections and infestations in the non-PNH placebo-controlled studies 5/526 in the Eculizumab group and 1/221 in the placebo group along with 18/458 in the non-PNH uncontrolled studies.

There was one patient who died in the SHEPHERD study (number 102-005). This patient is described in section 7.1 .1 of this review.

7.1.3.3 Other significant adverse events

In the TRIUMPH study 43/43 patients reported at least one adverse event in the Eculizumab treated group compared to 40/44 and the placebo group. In this study 4/43 Eculizumab treated patients compared to 9/44 placebo group patients reported at least one serious adverse event. In this study there was a higher percentage of mild adverse events reported in the Eculizumab group (84.1%) compared to the placebo group (78.3%). The table below shows the overview of treatment emergent adverse events in this study.

Table 17. Overview of Treatment-emergent Adverse Events (Safety)

	Eculizumab N = 43 n (%)	**Placebo N = 44 n (%)**
Overall number of events	226	277
Patients reporting at least 1 event	43 (100.0)	40 (90.9)
Patients reporting only 1 event	5 (11.6)	5 (11.4)
Patients reporting 2 events	5 (11.6)	5 (11.4)
Patients reporting 3 or more events	33 (76.7)	30 (68.2)
Patients reporting at least 1 SAE	4 (9.3)	9 (20.5)
Patients who withdrew due to an event	1 (2.3)	0 (0.0)
Number of events rated as:[a]		
Mild	190 (84.1)	217 (78.3)
Moderate	31 (13.7)	46 (16.6)
Severe	5 (2.2)	14 (5.1)
Unrelated	166 (73.5)	242 (87.4)
Possibly related	52 (23.0)	30 (10.8)
Probably related	7 (3.1)	5 (1.8)
Definitely related	1 (0.4)	0 (0.0)

[a] Intensity and relationship to study drug are on a per-event occurrence basis rather than on a per-patient basis.

Reference: Table 14.3.1

In the SHEPHERD study there were 599 events in 97 patients reported. Thus far 12/97 patients in this study have reported at least one serious adverse event. The sponsor reports, in this interim

analysis, that most of the adverse events have been mild (72.3%). The table below shows an overview of treatment emergent adverse events as of the interim analysis time.

Table 13. Overview of Treatment-Emergent Adverse Events (Safety)

	Eculizumab N = 97 n (%)
Overall number of events	599
Patients reporting at least 1 event	95 (97.9)
Patients reporting only 1 event	10 (10.3)
Patients reporting 2 events	20 (20.6)
Patients reporting 3 or more events	65 (67.0)
Patients reporting at least 1 SAE	12 (12.4)
Number of patients who died	1 (1.0)
Patients who withdrew due to an event	1 (1.0)
Number of events rated as:[a]	
Mild	433 (72.3)
Moderate	142 (23.7)
Severe	24 (4.0)
Unrelated	434 (72.5)
Possibly related	118 (19.7)
Probably related	46 (7.7)
Definitely related	1 (0.2)

[a] Severity and relationship to study drug are on a per-event occurrence basis rather than on a per-patient basis.

Reference: Table 14.3.1

7.1.4 Common Adverse Events

The table below shows the frequency of treatment emergent adverse events in ≥ 5% of the patient population in the TRIUMPH study. In this study 100% of Eculizumab treated patients compared to 90.9% of placebo group patients reported adverse events. In this study more Eculizumab treated patients developed the following adverse events: headache (44.2%), nasopharyngitis (23.3%), back pain (18.6%), nausea (16.3%), cough (11.6%), fatigue (11.6%), pruritus (7%), sinusitis (7%), constipation (7%), myalgia (7%), pain and extremity (7%), respiratory tract infection (7%) and herpes simplex (7%).

Table 18. Frequently (≥5%) Reported Treatment-emergent Adverse Events (Safety)

	Eculizumab N = 43		Placebo N = 44		Total N = 87	
Preferred Term	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events
Total	**43 (100.0)**	**226**	**40 (90.9)**	**277**	**83 (95.4)**	**503**
Headache	19 (44.2)	27	12 (27.3)	33	31 (35.6)	60
Nasopharyngitis	10 (23.3)	11	8 (18.2)	11	18 (20.7)	22
Upper respiratory tract infection	6 (14.0)	6	10 (22.7)	14	16 (18.4)	20
Back pain	8 (18.6)	9	4 (9.1)	7	12 (13.8)	16
Nausea	7 (16.3)	8	5 (11.4)	7	12 (13.8)	15
Cough	5 (11.6)	6	4 (9.1)	5	9 (10.3)	11
Diarrhoea	4 (9.3)	6	5 (11.4)	5	9 (10.3)	11
Arthralgia	3 (7.0)	4	5 (11.4)	6	8 (9.2)	10
Abdominal pain	2 (4.7)	2	5 (11.4)	6	7 (8.0)	8
Dizziness	2 (4.7)	2	5 (11.4)	9	7 (8.0)	11
Pharyngolaryngeal pain	3 (7.0)	3	4 (9.1)	4	7 (8.0)	7
Vomiting	2 (4.7)	2	5 (11.4)	6	7 (8.0)	8
Fatigue	5 (11.6)	13	1 (2.3)	1	6 (6.9)	14
Pruritus	3 (7.0)	3	3 (6.8)	3	6 (6.9)	6
Sinusitis	3 (7.0)	4	3 (6.8)	3	6 (6.9)	7
Viral infection	1 (2.3)	1	5 (11.4)	5	6 (6.9)	6
Constipation	3 (7.0)	3	2 (4.5)	2	5 (5.7)	5
Urinary tract infection	1 (2.3)	1	4 (9.1)	5	5 (5.7)	6
Contusion	1 (2.3)	1	3 (6.8)	5	4 (4.6)	6
Ear pain	1 (2.3)	1	3 (6.8)	4	4 (4.6)	5
Insomnia	1 (2.3)	1	3 (6.8)	3	4 (4.6)	4
Myalgia	3 (7.0)	3	1 (2.3)	1	4 (4.6)	4
Neutropenia	0 (0.0)	0	4 (9.1)	4	4 (4.6)	4
Pain in extremity	3 (7.0)	5	1 (2.3)	1	4 (4.6)	6
Paroxysmal nocturnal haemoglobinuria	1 (2.3)	1	3 (6.8)	5	4 (4.6)	6
Rash	1 (2.3)	1	3 (6.8)	3	4 (4.6)	4
Respiratory tract infection	3 (7.0)	4	1 (2.3)	3	4 (4.6)	7
Dyspnoea	0 (0.0)	0	3 (6.8)	3	3 (3.4)	3
Herpes simplex	3 (7.0)	3	0 (0.0)	0	3 (3.4)	3
Menorrhagia	0 (0.0)	0	3 (6.8)	3	3 (3.4)	3

Reference: Table 14.3.1.1

In the SHEPHERD study interim analysis the sponsor reports that the treatment emergent adverse events with highest reported frequency thus far are headache (49.5%) and nasopharyngitis (22.7%).

Table 14. Frequently (≥5%) Reported Treatment-Emergent Adverse Events (Safety)

	Eculizumab N=97	
Preferred term	**Patients n (%)**	**Events**
Total	95 (97.9)	599
Headache	48 (49.5)	74
Nasopharyngitis	22 (22.7)	27
Nausea	15 (15.5)	23
Upper respiratory tract infection	13 (13.4)	15
Pyrexia	12 (12.4)	15
Arthralgia	11 (11.3)	14
Abdominal pain	10 (10.3)	12
Dizziness	10 (10.3)	12
Constipation	8 (8.2)	9
Diarrhea	8 (8.2)	9
Back pain	7 (7.2)	10
Epistaxis	7 (7.2)	10
Myalgia	7 (7.2)	8
Urinary tract infection	7 (7.2)	8
Vomiting	7 (7.2)	23
Influenza-like illness	6 (6.2)	8
Fatigue	5 (5.2)	9
Herpes simplex	5 (5.2)	6
Rash	5 (5.2)	6

Reference: Table 14.3.1.1

7.1.4.1 Eliciting adverse events data in the development program

Patients underwent physical examination, had laboratories drawn according to the schedule of events and had routine follow-up visits according to the schedule of events listed in section 6 of this review.

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

The sponsor's categorization of adverse event is appropriate and based on MedRA preferred terms.

7.1.4.3 Incidence of common adverse events

Adverse events characterized by sponsors as to their relatedness to study drug are shown in the table in section 7.1.3.3 of this review. Only one adverse event in each of the TRIUMPH and SHEPHERD studies was considered by the investigator to be definitely related to Eculizumab.

7.1.4.4 Common adverse event tables

See section 7.1.4 common adverse event tables for the TRIUMPH and SHEPHERD studies.

7.1.4.5 Identifying common and drug-related adverse events

See section 7.1.4. Only one adverse event in each of the TRIUMPH and SHEPHERD studies was considered by the investigator to be definitely related to Eculizumab.

7.1.4.6 Additional analyses and explorations

Not applicable.

7.1.5 Less Common Adverse Events

The sponsor did not provide an analysis of less common adverse events. Narrative descriptions for the patients who died and who experienced meningococcal infections both in PNH and non-PNH studies are provided in the safety section (7) of this review.

Analyses of the infections for the TRIUMPH study are provided in the table below. This table shows that overall 26/43 Eculizumab treated patients compared to 28/44 placebo group patients reported at least one infection. In the Eculizumab treated patients 0/43 compared to 2/44 placebo treated patients developed severe infections. As is expected, 8/43 Eculizumab treated patients compared to 1/44 placebo group patients had infections possibly related to study drug.

Table 22. Summary of Treatment-emergent Infections (Safety)

	Eculizumab N=43 n (%)	Placebo N=44 n (%)
Patients reporting at least 1 infection	26 (60.5)	28 (63.6)
Patients reporting at least 1 serious infection	0 (0.0)	4 (9.1)
Number of infections reported - Overall	26 (60.5)	28 (63.6)
1	18 (41.9)	13 (29.5)
2	5 (11.6)	7 (15.9)
3 or more	3 (7.0)	8 (18.2)
Infection severity[a] - Overall	37	57
Mild	32 (86.5)	44 (77.2)
Moderate	5 (13.5)	11 (19.3)
Severe	0 (0.0)	2 (3.5)
Infection relation to study drug - Overall	37	57
Unrelated	29 (78.4)	56 (98.2)
Possible	8 (21.6)	1 (1.8)

[a] Only the most severe of the adverse events for each patient within each system organ class/preferred term was counted.

Reference: Table 14.3.1.1.3

Analyses of the infection rates so far reported in the SHEPHERD study are shown in the table below. This table shows that 71/97 patients so far have reported at least one infection, 2/97 patients reported severe infections and 0/97 patients were considered to have their infections definitely related to Eculizumab treatment.

Table 19. Summary of Treatment-Emergent Infections (Safety)

	Eculizumab N=97 n (%)
Patients reporting at least 1 infection	71 (73.2)
Patients reporting at least 1 serious infection	3 (3.1)
Number of patients reporting infections	
Overall	71 (73.2)
1	34 (35.1)
2	20 (20.6)
3 or more	17 (17.5)
Number of infections per severity	
Overall	140 (100.0)
Mild	103 (73.6)
Moderate	35 (25.0)
Severe	2 (1.4)
Infection relation to study drug	
Overall	140 (100.0)
Unrelated	130 (92.9)
Possible	10 (7.1)
Probable	0 (0.0)
Definitely	0 (0.0)

Reference: Table 14.3.1.1.3

7.1.6 Laboratory Findings

Laboratory findings in the TRIUMPH study showed the following:

- ALT- Median baseline values were 33.0 U/L for the Eculizumab treated patients compared to 34.0 U/L for the placebo group. At all subsequent visits median values for Eculizumab treated patients decreased below baseline levels (- 4.5U/L at visit 17) while placebo treated patients had an increase in ALT (3.0 U/L at visit 15).
- AST- In the Eculizumab treated patients median AST values were 121U/L compared to 129 U/L for the placebo group patients. Median values for Eculizumab treated patients decreased to levels within the normal range while placebo group patients showed an increase in AST.

- Haptoglobin- Some Eculizumab treated patients had a return to normal compared to no placebo group patients had a return to normal in their haptoglobin levels.
- Creatinine kinase- Creatinine kinase levels were elevated at baseline in both placebo and Eculizumab treated patients. The sponsor stated that this was attributed to the fact that creatinine kinase measurements using spectrophotometric methods and could have been falsely elevated when performed on hemolyzed samples. Baseline creatinine kinase level for the Eculizumab treated patients was at 113.0 U/L compared to 127.0 U/L for the placebo group which was within the normal range. At visit 18 again creatinine kinase level decreased in the Eculizumab treated patients (- 63 .0 U/L) compared to (21.0 U/L) at visit 15 in the placebo group.
- Bicarbonate- The sponsor reported that the influence of Eculizumab on bicarbonate levels was difficult to ascertain primarily due to the difference and handling of specimens at the various study sites worldwide. The sponsor reported that median bicarbonate values were no greater than 1.5 mmoL/L different between treatment groups at all scheduled laboratory evaluation visits after baseline. Most patients had below normal values at baseline and tended to remain below normal or increased to within normal range at subsequent visits after baseline.

7.1.6.1 Overview of laboratory testing in the development program

Laboratory testing was undertaken as per the schedule of events described in section 6 of this review.

7.1.6.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See section 7.1.6.

7.1.6.3 Additional analyses and explorations

In the TRIUMPH study flow cytometry was performed in order to determine the change from baseline in percentages type II and III clone sizes. The table below shows the change from baseline in percentages of type II and III red cell clones. At baseline there were no statistically significant differences between groups in type II or III red blood cells. At visit 18 the percentages of type II and type III PNH cells increased significantly. These data support the conclusion that protection of the PNH red blood cell from complement mediated hemolysis preserves the PNH red cell mass.

Table 25. Flow Cytometry Data: Change From Baseline in Percentages of Type II and III Cells (ITT)

Parameter		Eculizumab N=43	Placebo N=44	*P* Value[a]
Type II cells (%)				
Baseline Summary (Visit 1)	N	43	44	0.912029901
Mean (standard error)		7.7 (1.43)	8.7 (1.81)	
Median		3.6	4.0	
Range		(0.0, 41.5)	(0.0, 54.0)	
Change from Baseline at Visit 18	n	41	42	0.000264267
Mean (standard error)		4.3 (1.62)	0.2 (2.14)	
Median		1.4	-0.6	
Range		(-28.1, 33.1)	(-29.8, 79.6)	
Type III cells (%)				
Baseline Summary (Visit 1)	n	43	44	0.352551026
Mean (standard error)		31.6 (2.48)	36.2 (2.97)	
Median		28.9	32.9	
Range		(10.7, 79.0)	(6.8, 86.0)	
Change from Baseline at Visit 18	n	41	42	0.000000006
Mean (standard error)		25.9 (3.22)	-1.2 (2.29)	
Median		27.5	-0.5	
Range		(-25.1, 69.0)	(-54.4, 31.0)	

[a] *P* values were calculated using Wilcoxon's rank sum test.

Reference: Table 14.3.1.8

7.1.6.4 Special assessments

Not applicable.

7.1.7 Vital Signs

7.1.7.1 Overview of vital signs testing in the development program

The TRIUMPH study was the only placebo-controlled study in the development of Eculizumab for patients with PNH. There did not appear to be any trend or pattern with regard to blood pressure, heart rate, body temperature or body weight in terms of individual visit by visit fluctuations or intrapatient variations. There did not appear to be differences between the two treatment groups in terms of vital signs overall.

7.1.8 Electrocardiograms (ECGs)

Investigators in the TRIUMPH study were to conduct an ECG for patients and record the findings as normal, abnormal or not clinically significant or abnormal clinically significant. Statistical comparisons between treatment groups were not performed however, the number of patients having normal or abnormal ECG interpretations were similar at each of the evaluation time points. Only one Eculizumab treated patient (110-007, atrioventricular sequential pacemaker rhythm) and two placebo treated patients (110-003, signs of ischemia; 110-005, left ventricular hypertrophy) had abnormal clinically significant ECG findings. None of these resulted in any serious or non-serious treatment emergent adverse event. The sponsor reports that although there were outliers, most patients median findings appear to be within normal limits for PR interval, QRS duration, QT interval and ventricular heart rate.

7.1.8.1 Selection of studies and analyses for overall drug-control comparisons

The TRIUMPH study was the only placebo-controlled study in PNH patients.

7.1.9 Immunogenicity

In the TRIUMPH study immunogenicity was evaluated by determining the presence of IgG or IgM human antihuman antibody (HAHA) against Eculizumab. Only two patients demonstrated weak and transient responses to Eculizumab. These patients (number 110-001 and 110-003) had IgG reactions noted at visit 18. Patient 110-003 was in the placebo group and had a titer of 1:20 and 1:100 which were transient. Patient 110-001 had an IgG antibody titer of 1:20 on study day 182 and at that time the LDH was noted to be 265 U/L. Despite this low titer antibody to Eculizumab, the patient did not display a rebound in hemolysis over the course of the study as the LDH remained generally in the 200-300 U/L range and which remained below the baseline LDH (2728 U/L) for this patient .

In the SHEPHERD study there were two patients who developed antibodies to Eculizumab (number 101-001 and 180-003). Patient 101-001 had a low titer (1:20) IgG antibody identified at study day 365 and at that time the LDH was noted to be 276 U/L. On study day 491 the LDH was 470 U/L, which was the last reported LDH for this patient. Although the LDH for this patient increased to 470 U/L this was still within the range displayed by the patient during the treatment with Eculizumab (200-500 U/L) and the value remained below the baseline LDH (2703 U/L) for this patient. Patient 180-003 had two positive IgM titers reported on study day 36 (1:20) and study day 189 (1:100) respectively. The baseline LDH for this patient was 3054 U/L. On day 36 the LDH was reported to be 291 U/L and on day 189 the LDH was reported to be 297 U/L. After Day 189, the rest of this patient's LDH levels were in the 200-300 U/L range.

In the controlled non-PNH studies the incidences of 24-hour postinfusion adverse events were similar between patients treated with Eculizumab and patients treated with placebo (Eculizumab 49.2% compared to placebo 50.7%). The sponsor states that the same relationship is true for 48 hours post-infusion adverse events (Eculizumab 54.9% compared to placebo 56.6%). Immunogenicity was examined in all non-PNH clinical studies. The incidence of anti-

Eculizumab immune responses was 26/677 (3.8%) in Eculizumab treated patients compared to 11/206 (5.3%) placebo treated patients.

Therefore, it does not appear that patients who develop HAHA neutralizing antibodies to Eculizumab develop brisk rebound hemolysis. The database for patients exposed to Eculizumab is small and more patients would need to be exposed to determine the incidence of hemolysis after development of a neutralizing antibody.

7.1.10 Human Carcinogenicity

No formal human carcinogenicity testing was performed for Eculizumab. However, Eculizumab is highly species specific and therefore a surrogate mouse anti-murine C5 monoclonal antibody was used in toxicology studies. The sponsor reports that there were no treatment related effects or adverse event's in reproductive studies in mice with the surrogate antibody. In addition no treatment related adverse effects were seen in the long-term toxicity studies. In addition no general toxicity or proliferative activity is suggestive of carcinogenic risk were evident in these animal toxicity studies.

7.1.11 Special Safety Studies

In the TRIUMPH study meningococcal vaccine titer samples were collected. All patients had detectable levels of quantitative serum IgG after vaccination.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

It is not expected that Eculizumab will be abused due to the fact that the sponsor states in the proposed labeling that Eculizumab should be administered by a qualified health professional. See section 7.1.15 for discussion of withdrawal phenomena.

7.1.13 Human Reproduction and Pregnancy Data

No studies of Eculizumab on human reproduction or pregnancy have been performed. However one patient did become pregnant while on treatment with Eculizumab in the TRIUMPH study as described previously. This patient subsequently had a normal pregnancy and delivery.

7.1.14 Assessment of Effect on Growth

All patients enrolled in PNH studies were age $\geq$ 18 years (range 18-85 years). No assessment on growth has been performed.

7.1.15 Overdose Experience

There is no overdose potential for treatment with Eculizumab as the sponsor states in the proposed labeling that the drug should be administered by a qualified health professional. There were no cases of overdose reported during the clinical studies for Eculizumab. There is no

known deleterious effect of overdose of Eculizumab. PNH patients who had been withdrawn from Eculizumab due to adverse events have shown a return over a period of approximately 1 month to baseline hemolysis levels. No rebound effect has been described in the studies were patients have had a progressive increase in their PNH red blood cell clone and where subsequently discontinued from study while still requiring treatment with Eculizumab. The table below shows the data from patient 028-003 from the TRIUMPH study. This patient was discontinued secondary to pregnancy after having received three months of Eculizumab treatment. The table demonstrates that during the time of treatment the patient's type III red blood cell clone increased from 49.8% to 72.1%. After having discontinued the study drug the patient's type III red blood cell clone percentage decreased back towards baseline. The patient's hemoglobin also decreased back towards her baseline of 7.9 g/dl. This table supports the fact that there does not appear to be a precipitous hemolytic rebound effect after having discontinued Eculizumab therapy.

Date	Study Day	Red blood cells (10^{12}/L)	Hemoglobin (g/dL)[a]	Hematocrit (volume fraction)	Type III cells (%)
28 Feb 2005	1[b]				
14 Mar 2005	15				
28 Mar 2005	29				
26 Apr 2005	58				
23 May 2005	85				
Follow-up laboratory values after study drug discontinuation:					
08 Jun 2005	101				
14 Jun 2005	107				
15 Jun 2005	108				
30 Jun 2005	123				
26 Jul 2005	149				

[a] Her hemoglobin set point was
[b] Study day 1 is the date of first dose of study drug
[c] Received 1 unit of PRBCs
Reference: Listing 16.2.5.1.0, Listing 16.2.7.1.2, and Listing 16.2.7.4.2

7.1.16 Postmarketing Experience

Eculizumab is a new molecular entity and has not been marketed anywhere in the world at present.

7.2 Adequacy of Patient Exposure and Safety Assessments

The TRIUMPH study was adequately designed to permit an evaluation for both efficacy and safety in the described population. In addition, the SHEPHERD study provides additional information for the safety database. The remainder of the uncontrolled clinical studies in PNH patients treated with Eculizumab support the safety profile of Eculizumab.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The sponsor provided narratives for patient deaths and infections for the patient's treated with Eculizumab or placebo both in the PNH and non-PNH settings.

7.2.1.1 Study type and design/patient enumeration

The studies used in the analysis for safety are described in section 4.1.

7.2.1.2 Demographics

In the multiple dose double-blind placebo-controlled non-PNH studies, 65.2% of Eculizumab treated patients were women, 80.4% Caucasian and 80.2% were 18-<65 years of age. The median weight was 81.2 kg. In the placebo treated group 661% of patients were women, 81% Caucasian, 75.6% were 18-<65 years of age. The median weight was 77.1 kg.

The demographic patterns of patients enrolled in multiple dose uncontrolled non-PNH studies were generally similar to those from the double-blind placebo-controlled non-PNH studies. This was expected because all uncontrolled non-PNH studies were extension studies to the double-blind placebo-controlled studies. In the multiple dose uncontrolled non-PNH studies 67.5% of patients were women, 81.0% were Caucasian, 77.7% of or 18-<65 years of age and the median weight was 82.8 kg.

In the PNH population there were some differences and baseline demographic parameters for Eculizumab and placebo treated patients in the TRIUMPH study and the SHEPHERD study. Most of the differences in demographics are likely due to either small sample sizes or differences in enrollment criteria between the studies. The table below shows the summary of study demographics between the TRIUMPH and SHEPHERD studies. Fewer patients in the TRIUMPH study had a history of aplastic anemia (14% compared to 28.9% in the SHEPHERD study). The small differences in demographic parameters in the SHEPHERD study compared to the TRIUMPH study reflect the broader inclusion criteria for the SHEPHERD study. The SHEPHERD study had more patients with a history of thrombosis, fewer patients with a baseline platelet count of > 100,000/ml, fewer patients with a baseline hemoglobin > 8.0 g/dl, more patients with baseline PNH type III red blood cells > 50%, fewer patients with > 4 red blood cell units transfused per year.

Sponsor Table 2.7.4.1.3.2.2-1 Summary of Phase 3 PNH Study Demographics

	TRIUMPH		SHEPHERD
Parameter	Placebo N = 44	Eculizumab N = 43	Eculizumab N = 97
Mean Age (SD)	38.4 (13.4)	42.1 (15.5)	41.1 (14.4)
Gender - Female (%)	29 (65.9)	23 (53.5)	49 (50.5)
History of AA or MDS (%)	12 (27.3)	8 (18.7)	29 (29.9)
Concomitant Anticoagulants (%)	20 (45.5)	24 (55.8)	59 (60.8)
Concomitant Steroids (%)	16 (36.4)	14 (32.6)	46 (47.4)
Median PRBC in previous 12 months	17.0	18.0	8.0 1
Mean Hgb	7.7 (0.75)	7.8 (0.79)	N/A
Pre-treatment LDH levels	2,234.5	2,032.0	2,051.0
Free Hemoglobin at baseline	46.2	40.5	34.9

7.2.1.3 Extent of exposure (dose/duration)

The total patient exposure to Eculizumab by dose regimen is shown in the table below.

Table 2.7.4.1.2.2-1: Total Patient Exposure to Eculizumab by Duration of Dosing and Dosage Regimen[7]

Duration of Dosing (weeks)	Dosage Regimens						
	A[1]	B[2]	C[3]	D[4]	E[5]	X[6]	Total
≤ 4	11	0	17	23	0	50	101
> 4 to ≤ 12	23	2	24	45	4	0	98
> 12 to ≤ 26	36	12	46	55	53	0	202
> 26 to ≤ 39	8	2	12	18	83	0	123
> 39 to ≤ 52	14	0	14	14	16	0	58
> 52 to ≤ 78	79	11	108	90	28	0	316
> 78 to ≤ 104	0	0	0	1	1	0	2
> 104 to ≤ 156	0	0	1	0	0	0	1
> 156	0	0	0	0	10	0	10

[1] A = 8 mg/kg Q2 wks; or 600 mg Q2 wks
[2] B = 8 mg/kg Q4 wks, or 600 mg Q4 wks
[3] C = 8 mg/kg Q wk for 5 wks, then Q4 wks; or 600 mg Q wk for 5 wks, then Q4 wks
[4] D = 8 mg/kg Q wk for 5 wks, then Q2 wks; or 600 mg Q wk for 5 wks, then Q2 wks
[5] E = 600 mg Q wk for 4 wks, then 900 mg on wk 5, then 900 mg Q2 wks.
[6] X = 0.1mg/kg to 8.0 mg/kg
[7] Source: Table 2.7.4.7-5

The table below shows the patient exposure to Eculizumab in terms of the number of weeks of exposure in PNH and non-PNH patients who had multiple doses of drug. There have been 57 patients exposed to the proposed Eculizumab dosing regimen for PNH patients described in this review for a period up to 26 weeks. Ninety-nine PNH patients exposed to the proposed regimen have had an exposure from 26 to 52 weeks. Thirty-nine PNH patients have been exposed to the proposed regimen for more than 52 weeks. The table below shows the total patient exposure to Eculizumab by duration of dosing and dosage regimen.

Table 2.7.4.1.2.2-2: Overview of Patient Exposure to Eculizumab, Multiple Doses[1]

Exposure (weeks)	Non-PNH Pts Exposed (Regimens A, B, C, or D)	PNH Pts Exposed (Regimen E)	Total Exposure (Unique Pts)	Summary Exposure
0 to ≤ 26	294	57	351	351
> 26 to≤ 52	82	99	181	510
> 52	290	39	329	

[1]Source: Table 2.7.4.7-5

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The safety database was evaluated for all PNH studies listed in section 4.1 of this review.

7.2.2.1 Other studies

As noted in the safety section of this review other studies that have been evaluated for safety include the non-PNH studies as listed previously in section 4.1 of this review.

7.2.2.2 Postmarketing experience

Not applicable as Eculizumab has not been marketed in the United States or any other country previously.

7.2.2.3 Literature

Study CO2-001 and C 04-001 have been published:

- CO2-001 – Hillmen, P et al.: Effect of Eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. NEJM. 2004; 350: 552-558.
- C04-001 – Hillmen, P et al.: The compliment inhibitor Eculizumab in paroxysmal nocturnal hemoglobinuria. NEJM. 2006; 355: 1233-1243.

7.2.3 Adequacy of Overall Clinical Experience

The TRIUMPH study was carried out in a randomized controlled fashion for a period of 26 weeks allowing adequate analysis of the clinical experience. In addition the SHEPHERD study was carried out with a treatment phase of 52 weeks allowing additional analysis of the Eculizumab safety profile. Additional analysis of the Eculizumab safety profile was undertaken

by examining the other uncontrolled PNH studies and the other non-PNH studies which are listed in section 4.1 of this review.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

7.2.5 Adequacy of Routine Clinical Testing

The TRIUMPH study analyzed the appropriate endpoints and safety data. In addition the SHEPHERD and other studies allowed for additional analysis of the safety profile of Eculizumab.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No formal analysis of drug interaction was undertaken in the TRIUMPH study. However, patients in the TRIUMPH study were treated with a number of concomitant medications as listed in the table below.

Table 8. Summary of Concomitant Medications Taken by at Least 5% of Patients in Either Treatment Group (ITT)

Anatomical therapeutic chemical classification level 2 term	Eculizumab N = 43 n (%)	Placebo N = 44 n (%)
Vaccines	43 (100)	44 (100)
Antianemic preparations	31 (72.1)	36 (81.8)
Analgesics	30 (69.8)	29 (65.9)
Antithrombotic agents	24 (55.8)	20 (45.5)
Antibacterials for systemic use	23 (53.5)	26 (59.1)
Corticosteroids for systemic use	13 (30.2)	15 (34.1)
Antacids, drugs for treatment of peptic ulcers and flatulence	12 (27.9)	11 (25.0)
Antihistamines for systemic use	9 (20.9)	15 (34.1)
Vitamins	9 (20.9)	8 (18.2)
Psycholeptics	8 (18.6)	9 (20.5)
All other therapeutic products	6 (14.0)	7 (15.9)
Blood substitutes and perfusion solutions	6 (14.0)	4 (9.1)
Psychoanaleptics	6 (14.0)	4 (9.1)
Laxatives	6 (14.0)	6 (13.6)
Mineral supplements	6 (14.0)	8 (18.2)
Antiinflammatory and antirheumatic products	6 (14.0)	10 (22.7)
Beta blocking agents	5 (11.6)	2 (4.5)
Antidiarrheal, intestinal antiinflammatory/antiinfective agents	4 (9.3)	4 (9.1)
Antispasmodics and anticholinergic agents and propulsives	4 (9.3)	4 (9.1)
Sex hormones and modulators of the genital system	4 (9.3)	8 (18.2)
Agents acting on the renin-angiotensin system	4 (9.3)	1 (2.3)
Cough and cold preparations	4 (9.3)	9 (20.5)
Antibiotics and chemotherapy for dermatological use	3 (7.0)	1 (2.3)
Antivirals for systemic use	3 (7.0)	1 (2.3)
Corticosteroids, dermatological preparations	3 (7.0)	1 (2.3)
Nasal preparations	3 (7.0)	2 (4.5)
Diuretics	3 (7.0)	3 (6.8)
Ophthalmologicals	3 (7.0)	3 (6.8)
Calcium channel blockers	2 (4.7)	3 (6.8)
Antiasthmatics	1 (2.3)	3 (6.8)
Drugs for treatment of bone diseases	1 (2.3)	3 (6.8)
Anesthetics	0 (0.0)	5 (11.4)

Reference: Table 14.1.3.1

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor's evaluation of the potential adverse events is adequate given the number of studies undertaken in the PNH and non-PNH settings. The sponsor should continue to monitor postmarketing experience as is required in 21 CFR § 314.50 (d) (5) (vi) (b). The sponsor also proposes a risk minimization program for infections and also includes a black box warning in the proposed labeling indicating the potential for *Neisseria meningitidis* infection and the need for prior vaccination for *Neisseria meningitidis*.

7.2.8 Assessment of Quality and Completeness of Data

The sponsor has presented a complete safety profile and complete data for the TRIUMPH study. For the SHEPHERD study the sponsor has presented an adequate analysis of the 26 week interim data. The SHEPHERD study is ongoing. In addition the sponsor has an ongoing extension study as is listed in section 4.1 in this review.

7.2.9 Additional Submissions, Including Safety Update

Amendment 4 of this BLA submission contained updated safety information. The sponsor should continue to monitor ongoing studies and, after approval, postmarketing adverse events as is required in 21 CFR § 314.50 (d) (5) (vi) (b).

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Headache was the most common adverse event observed in the TRIUMPH and SHEPHERD studies. This adverse event was described in more detail in section 7.1.4.

Infection with *Neisseria meningitidis* is concerning because this infection can be fatal if not treated quickly and with appropriate antibiotics. There have been three Eculizumab treated patients with *Neisseria meningitidis* infection (two vaccinated PNH patients and one unvaccinated non-PNH patient). The sponsor proposes a risk minimization program for this infection. Also, the proposed labeling contains information in a black box warning regarding the potential for *Neisseria meningitidis* infection and the need for vaccination. This adverse event was described in this review in section 7.1.2.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The table below shows the incidence of adverse events across all PNH studies. The adverse events reported in the TRIUMPH and SHEPHERD studies were discussed throughout section 7 of this review. Overall, in 193 patients in the uncontrolled study database, which does not include the one patient in the physician sponsored IND submitted after the BLA submission, the sponsor reports that 99.0% (191/193) of patients experienced at least one adverse event and that 30.6% (59/193) of patients had at least one serious adverse event. Overall, most adverse events associated with Eculizumab treatment were mild to moderate in severity. Serious adverse events by preferred term in more than 2% of the patients in the 193 patient uncontrolled database, which does not include the one patient in the physician sponsored IND submitted after the BLA submission, were: pyrexia 3.6% (7/193), viral infection 3.1% (6/193), anemia 2.1% (4/193) and headache 2.1% (4/193). Adverse events by preferred term reported in more than 10% of the patients in the 193 patient uncontrolled study database, which does not include the one patient in the physician sponsored IND submitted after the BLA submission, were: headache 52.8% (102/93), nasopharyngitis 39.9% (77/193), upper respiratory tract infection 28.5% (55/193),

nausea 22.8% (44/193), pyrexia 18.1% (35/193), arthralgia 18.1% (35/193), back pain 17.6% (34/193), diarrhea 17.1% (33/193), vomiting 15.5% (30/193), dizziness 15.0% (29/193), cough 14.5% (28/193), pharyngolaryngeal pain 13.0% (25/193), pain in extremity 12.9% (25/193), influenza-like illness 12.4% (24/193), abdominal pain 11.9% (23/193), insomnia 11.9% (23/193), viral infection 11.4% (22/193), constipation 10.9% (21/193), urinary tract infection 10.9% (21/193), contusion 10.9% (21/193) and myalgia 10.3% (20/193).

Table 5.3.5.3.2.3.2-1 Overall Summary of Treatment Emergent Adverse Events in Multiple-Dose, Double-Blind Placebo-Controlled and Uncontrolled PNH Clinical Studies

		C04-001		C04-002	C04-001/ C04-002	E05-001 [1]	All Uncontrolled Studies [2]
	Description	Eculizumab (N = 43)	Placebo (N = 44)	Eculizumab (N = 97)	Eculizumab (N = 140)	Eculizumab (N = 71)	Eculizumab (N = 193)
Patients	At Least One TEAE	43 (100.0%)	40 (90.9%)	95 (97.9%)	138 (98.6%)	71 (100.0%)	191 (99.0%)
	At Least One SAE	4 (9.3%)	9 (20.5%)	19 (19.6%)	23 (16.4%)	17 (23.9%)	59 (30.6%)
	Withdrawal due to TEAEs	1 (2.3%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (1.4%)	1 (0.5%)
	Number of Patients Died	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.7%)	1 (1.4%)	2 (1.0%)
Total number of TEAEs		226	277	965	1191	806	2887
Number of patients reporting	1 TEAE	5 (11.6%)	5 (11.4%)	0 (0.0%)	5 (3.6%)	4 (5.6%)	0 (0.0%)
	2 TEAEs	5 (11.6%)	5 (11.4%)	11 (11.3%)	16 (11.4%)	3 (4.2%)	11 (5.7%)
	3+ TEAEs	33 (76.7%)	30 (68.2%)	84 (86.6%)	117 (83.6%)	64 (90.1%)	180 (93.3%)
TEAE Intensity	Mild	190 (84.1%)	217 (78.3%)	698 (72.3%)	888 (74.6%)	645 (80.0%)	1939 (67.2%
	Moderate	31 (13.7%)	46 (16.6%)	232 (24.0%)	263 (22.1%)	125 (15.5%)	476 (16.5%)
	Severe	5 (2.2%)	14 (5.1%)	35 (3.6%)	40 (3.4%)	36 (4.5%)	103 (3.6%)
	Overall	226 (100.0%)	277 (100.0%)	965 (100.0%)	1191 (100.0%	806 (100.0%)	2887 (100.0%
TEAE Relationship to Study Drug [3]	I	166 (73.5%)	242 (87.4%)	734 (76.1%)	900 (75.6%)	712 (88.3%)	2391 (82.9%
	II	60 (26.5%)	35 (12.6%)	231 (23.9%)	291 (24.4%)	94 (11.7%)	496 (17.2%)

[1] Includes C04-001 patients who completed 12 months in E05-001
[2] Includes C02-001, E02-001, X03-001, C04-002 and E05-001
[3] I = Not related or unlikely to be related; II = Possibly, probably or definitely related.

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In the PNH studies, two patients developed *Neisseria meningitidis* infection.

Currently there is no information available regarding the one patient from the physician sponsored IND which was opened after the BLA submission.

7.4.2 Explorations for Predictive Factors

Eculizumab blocks the C-5 mediated terminal complement cascade which is important in the prevention of infection with encapsulated organisms. Patients who are exposed to Eculizumab are at an increased risk for infections with encapsulated organisms. Neisseria meningitidis poses the greatest risk due to infection with this organism can rapidly progress and cause death if not recognized and treated early.

The sponsor reported that 88.1% (170/193) of patients in the 193 patient uncontrolled database, which does not include the one patient in the physician sponsored IND submitted after the BLA

submission, had infection related adverse events. However the rate of other encapsulated organism infection was low. In this database 3/193 (1.6%) had infection reported as beta hemolytic streptococcus infection, hemophilus infection or streptococcal sepsis. The database for Eculizumab in PNH patients is small and the sponsor should continue to evaluate for infections with encapsulated organisms as part of a postmarketing commitment as described in section 1.2.2 of this review.

7.4.3 Causality Determination

Eculizumab blocks the C-5 mediated terminal complement cascade which is important in the prevention of infection with encapsulated organisms. There were three cases of *Neisseria meningitidis* infection in the PNH studies. As Eculizumab is designed to interrupt normal immune function by blocking the C-5 mediated terminal complement cascade in patients the cause for these *Neisseria meningitidis* infections can be directly linked to Eculizumab. In the PNH studies the sponsor incorporated an early alert program in order to minimize the risk of infection with *Neisseria meningitidis*. In addition the sponsor proposes a black box warning to highlight the increased risk of *Neisseria meningitides* infection with Eculizumab.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing of Eculizumab in PNH patients has been evaluated in the TRIUMPH study, SHEPHERD study and other uncontrolled PNH studies. The dosing regimen proposed is Eculizumab a 600 mg IV infusion every 7 +/- 2 days for the first four weeks then 900 mg for the 5th dose 7 +/- two days later than 900 mg every 14 +/- 2 days thereafter. This dosing regimen was found to have the necessary concentration to completely block the terminal complement cascade. The intravenous infusion should be given over [redacted] minutes.

8.2 Drug-Drug Interactions

No drug-drug interaction analysis was undertaken. Patients treated with Eculizumab in the PNH studies were also treated with various concomitant medications.

8.3 Special Populations

The sponsor proposes that Eculizumab be indicated for the treatment of PNH [redacted]

extension studies in patients with PNH as are listed in section 4.1 of this review. The use of Eculizumab in patients with PNH whose age is < 18 years has not been studied.

Patients treated with Eculizumab in the TRIUMPH study showed improvement in AST, ALT and creatinine kinase compared to baseline levels. Separate analysis of a possible negative effect

of Eculizumab on levels of liver transaminases or creatinine in patients with hepatic or renal insufficiency would likely be difficult due to the improvement that was observed in these parameters in patients who generally have background elevation in liver transaminases and creatinine due to the underlying hemolysis in PNH.

8.4 Pediatrics

Eculizumab for the treatment of patients with PNH was not studied in patients whose age was < 18 years. Cases of PNH and the pediatric setting have been described. However, Eculizumab was granted Orphan Drug Designation (ODD # 03-1732) on August 20, 2003 for the treatment of PNH. The sponsor requests an exemption from the requirement to assess this product in pediatric PNH subpopulations pursuant to 21 CFR § 601.27 (d) given the rarity of PNH in general and the fact that only case reports have been listed for pediatric patients. The sponsor should be granted the exemption.

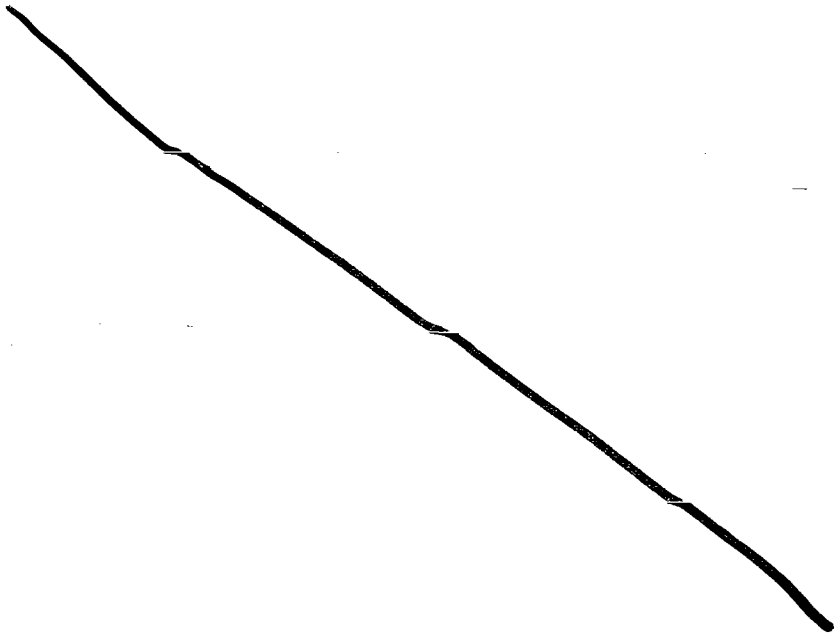
8.5 Advisory Committee Meeting

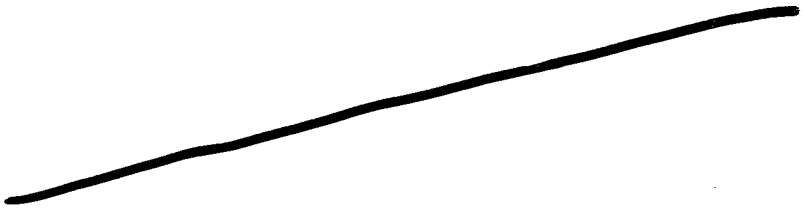
Not applicable.

8.6 Literature Review

As noted in section 7.2.2.3 there have been 2 published studies of Eculizumab for the treatment of patients with PNH.

8.7 Postmarketing Risk Management Plan





8.8 Other Relevant Materials

- SEALD Consult: The results of the SEALD consult are discussed in section 6.1.4 of this review. These recommendations are reflected in the wording in section 9.4 of this review and section 10.3 of this review which shows the proposed draft label.
- CMC Review: The results of the CMC review are discussed in 1.2.2 and 3.1 of this review.
- DMETS Consult: The result of this consult was that the sponsor could use the name trade name Soliris for marketing of the drug Eculizumab.
- Maternal Health Team Consult: The results of this consult are shown in the wording of the draft labeling in section 10.3 of this review.
- Statistics and Clinical Pharmacology reviews were also done.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor has demonstrated in an adequate and well controlled study (TRIUMPH) that Eculizumab is effective in the treatment of patients with transfusion dependent PNH by decreasing hemolysis [redacted] It also appears that Eculizumab may improve QOL in patients with PNH in terms of decreasing fatigue and by improving other QOL parameters. Due to the fact that a large number of patients were on concomitant anticoagulant therapy a conclusion regarding Eculizumab's effect on thrombosis incidence rates cannot be made.

There were 7 deaths in all of the Eculizumab studies combined. No deaths occurred in the TRIUMPH study. There were three deaths in non-PNH studies and four deaths in PNH studies other than the TRIUMPH study.

In the TRIUMPH study 4/43 patients in the Eculizumab group compared to 9/44 patients in the placebo group had serious adverse events. The most prevalent serious adverse event was exacerbation of PNH which occurred and one Eculizumab treated patient and three placebo treated patients.

In addition, overall one Eculizumab treated patient reported one serious adverse event associated with infection compared to four placebo patients who reported six infection-related serious

adverse events. Overall, there were three patients who developed meningococcal infection while enrolled in the Eculizumab trials (two PNH patients and one non-PNH patient). In the PNH trials there were two patients who discontinued treatment prematurely. Neither of these discontinuations appeared to be related to Eculizumab treatment (one patient with pregnancy, one patient with myelodysplastic syndrome).

Overall, in 193 patients in the uncontrolled study database, which does not include the one patient in the physician sponsored IND submitted after the BLA submission, the sponsor reports that 99.0% (191/193) of patients experienced at least one adverse event and that 30.6% (59/193) of patients had at least one serious adverse event. Overall, most adverse events associated with Eculizumab treatment were mild to moderate in severity. Serious adverse events by preferred term in more than 2% of the patients in the 193 patient uncontrolled database, which does not include the one patient in the physician sponsored IND submitted after the BLA submission, were: pyrexia 3.6% (7/193), viral infection 3.1% (6/193), anemia 2.1% (4/193) and headache 2.1% (4/193). Adverse events by preferred term reported in more than 25% of the patients in the 193 patient uncontrolled study database, which does not include the one patient in the physician sponsored IND submitted after the BLA submission, were: headache 52.8% (102/93), nasopharyngitis 39.9% (77/193), upper respiratory tract infection 28.5% (55/193).

In the PNH studies three patients developed human antihuman antibodies (HAHA) after treatment with Eculizumab. Two patients had IgG titers of 1:20 and one patient had IgM titers of 1:20 and 1:100. None of these patients developed a rebound in hemolysis despite the presence of these neutralizing antibodies.

Therefore, Eculizumab appears to be generally safe for the treatment of patients with PNH. However, because of the mechanism of action of Eculizumab on the immune system, patients with PNH who are treated with Eculizumab are at increased risk for infections with encapsulated organisms. The sponsor proposes an early alert program and a registry program in order to minimize the risk of infections in patients with PNH were treated with Eculizumab. In addition patients who are to be treated with Eculizumab must be vaccinated with *Neisseria meningitidis* vaccine at least two weeks prior to treatment with Eculizumab as was described in the protocols in the PNH studies.

9.2 Recommendation on Regulatory Action

The indication sought by the sponsor for the treatment of PNH [redacted] should be approved. The Eculizumab dosing regimen is:

- 600 mg of Eculizumab administered every week for the first four weeks, 900 mg of Eculizumab administered in week five and 900 mg dose of Eculizumab every 14 +/- 2 days thereafter. The drug is administered as a [redacted] minute intravenous (IV) infusion.

9 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2

REFERENCES

[1] http://www.emedicine.com/med/topic2696.htm
[2] Lichtman, M.A. et al.: Williams Manual of Hematology sixth edition. 2003.
[3] Mallinson, T. et al.: Giving meaning to measure: linking self-reported fatigue and function to performance of everyday activities. J. Pain Symp. Manage. 2006. 31(3): 229-241.
[4] Schillinger, J. A. et al.: National seroprevalence and trends in herpes simplex virus type 1 in the United States, 1976-1994. Sex Transm Dis. 2004. 31 (12): 753-760.

9.3 Recommendation on Postmarketing Actions

- The sponsor should continue to monitor adverse events as required by 21 CFR § 314.50 (d) (5) (vi) (b).
- See section 1.2.2 of this review for a list of the recommended postmarketing commitments.

9.3.1 Risk Management Activity

The sponsor should institute their risk minimization program for meningococcal infection.

9.3.2 Required Phase 4 Commitments

See section 9.3.

9.3.3 Other Phase 4 Requests

See section 9.3.

9.4 Labeling Review

A draft label was submitted by the sponsor in this BLA submission. Below is attached a label containing changes to the sponsor's proposed label which incorporates wording that is based on this review of the BLA submission.

- The sponsor should include the proposed black box warning which contains wording reflecting the potential for *Neisseria meningiditis* infection, the need for *Neisseria meningiditis* vaccination and enrollment in the sponsor's registry program.
- The INDICATIONS AND USAGE section of the label should contain the wording that Eculizumab is indicated for treatment of patients with PNH [redacted]
- The ADMINISTRATION section of the label should contain the wording that patients should be monitored for at least one hour following the completion of infusion of Eculizumab.
- The LABORATORY MONITORING section of the label should contain wording that adequately describes the Eculizumab discontinuation protocol. This wording should include wording that states that the physician should monitor for potential life-threatening hemolysis:

    - ≥ 25% decrease in type III PNH red blood cells.
    - A decrease in hemoglobin to 5 g/dl or ≥ 4 g/dl decrease in one week.
    - Angina.
    - Change in mental status.
    - 50% increase in serum creatinine.
    - Thrombosis.

- Follow-up visits at 1, 2, 4, and eight weeks after the discontinuation of Eculizumab.

- The IMMUNOGENICITY section of the label should state that infrequent low titer antibody responses have been detected with Eculizumab.
- The IMMUNIZATION section should contain wording that PNH patients must receive *N. meningiditis* vaccinations according to current immunization guidelines at least two weeks prior to receiving Eculizumab.
- The ADVERSE REACTIONS section of the label should include data from the TRIUMPH study and adverse reactions for all PNH patients exposed to Eculizumab.
- The CLINICAL STUDY section of the label should not include thrombosis or quality-of-life measures for the following reasons:

  - Thrombosis was an exploratory endpoint and approximately 50% of the patients in the controlled TRIUMPH study were concomitantly treated with anticoagulants thereby confounding the effect of Eculizumab on the rate of thrombosis. Similarly, a majority of patients (59/97) were on concomitant anticoagulant therapy in the SHEPHERD study.
  - [redacted]

9.5 Comments to Applicant

The indication sought by the sponsor may be approved provided the recommended changes are made in the proposed labeling and postmarketing commitments as presented in section 1.2.2 of this review are undertaken. The sponsor should continue to report on the safety and efficacy of Eculizumab in the PNH population as required by 21 CFR § 314.50 (d) (5) (vi) (b).

10 APPENDICES

10.1 Review of Individual Study Reports

The studies used for this review are listed in section 6.0 of this review.

10.2 Line-by-Line Labeling Review

The proposed draft labeling based on this review is shown below.

10.3 Proposed Product Label

The proposed draft labeling is shown below.