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125166

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA; STN	125166/0000
Submission Date(s)	9/15/06
PDUFA Due Date	3/16/07 (6-month priority review)
Brand Name	Soliris
Generic Name	Eculizumab
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Sponsor	Alexion Pharmaceuticals
Relevant IND(s)	BB-IND 11,075
Submission Type	Original BLA (NME, first in class)
Formulation	Solution for intravenous infusion
Proposed indication	Treatment of paroxysmal nocturnal hemoglobinuria
Proposed Dosage and Administration	600 mg every 7 days for 4 doses, followed by 900 mg for the fifth dose 7 days later, then 900 mg every 14 days thereafter, via intravenous infusion over <u> </u> minutes

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1 EXECUTIVE SUMMARY

Eculizumab (Soliris[®]) being developed by Alexion Pharmaceuticals is a humanized monoclonal antibody that binds to the human C5 complement protein and inhibits terminal complement-mediated cell lysis. In this original BLA for the approval of eculizumab, the proposed indication is the treatment of paroxysmal nocturnal hemoglobinuria (PNH) for which the Sponsor received an orphan drug designation. The 6-month priority review requested by the Sponsor was granted to this submission.

1.1 Recommendation

From a clinical pharmacology standpoint, this BLA is acceptable for the approval of eculizumab for the treatment of adult PNH patients. The labeling texts are under negotiation at the time of completion of this review. Initial labeling recommendations for clinical pharmacology sections are in Section 3 DETAILED LABELING RECOMMENDATIONS.

1.2 Phase 4 Study Commitments

No Phase 4 Commitments are recommended from a clinical pharmacology standpoint.

1.3 Summary of Clinical Pharmacology Findings

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 membranous 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).

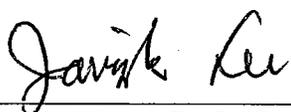
Basic Pharmacokinetics

- 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 \pm 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.

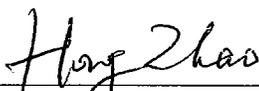
Immunogenicity

- Using a partially validated enzyme-linked 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.



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2 QUESTION-BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Eculizumab is a recombinant humanized monoclonal IgG2/4 κ antibody that binds to the human C5 complement protein and inhibits the activation of terminal complement. The eculizumab antibody contains human constant regions and murine complementarity-determining regions grafted onto the human framework light- and heavy-chain variable regions. The antibody is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kD.

Eculizumab is produced in a murine myeloma (NS0 cell line) expression system and purified by affinity and ion exchange chromatography. The drug substance manufacturing process includes ~~_____~~. The final eculizumab product is a sterile, clear, colorless, preservative-free 10 mg/mL solution for intravenous (IV) infusion and is supplied in 30-mL single-use vials. The product is formulated at pH 7.0 and each vial contains eculizumab 300 mg, sodium phosphate monobasic 13.8 mg, sodium phosphate dibasic 53.4 mg, sodium chloride 263.1 mg, polysorbate 80 6.6 mg (vegetable origin) and USP Water for Injection.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired genetic deficiency of endogenous complement inhibitors. A genetic mutation in patients with PNH leads to the generation of populations of abnormal blood cells, referred to as PNH cells that are deficient in terminal complement inhibitor protein (CD59), rendering PNH red blood cells (RBC) sensitive to persistent terminal complement-mediated destruction. The subsequent intravascular hemolysis is the primary disease manifestation in PNH patients and contributes to the morbidities and mortality in PNH patients. The destruction and loss of these PNH cells results in reduction in RBC mass (anemia), fatigue, difficulty in functioning, pain, dark urine, shortness of breath, and abnormal coagulation. Severe anemia requiring transfusion is a serious morbidity, as refractory transfusion-dependent hemolytic anemia is considered a major complication of PNH. Life-threatening thromboembolism (TE) in PNH is often directly associated with intravascular hemolysis in PNH and is induced by the release of free hemoglobin, consumption of nitric oxide, and subsequent clotting.

There are no therapies specifically approved for the treatment of PNH. Current treatments for PNH are palliative and do not address the underlying disease process, intravascular hemolysis. Vitamin and mineral supplementation, and erythropoietin stimulating agents have been used to increase RBC production; however, increased production of complement-inhibitor deficient PNH RBCs would be expected to increase, not decrease, intravascular hemolysis. Blood transfusions do not treat intravascular hemolysis and may only transiently improve some anemia-related symptoms. Refractory transfusion-dependent hemolytic anemia is an indication for bone marrow transplantation. Corticosteroid and androgen therapy may be utilized in PNH, but no controlled data exist to suggest clinical benefit or whether any potential benefit outweighs the established

risks of such therapies. Bone marrow transplantation may be considered, but is restricted to a limited number of patients. Anti-coagulant therapy has been recommended for prophylaxis and treatment of TE in PNH, although no controlled trials have examined whether the benefit outweighs the risk of hemorrhage.

Eculizumab is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Eculizumab therefore restores terminal complement regulation in the blood of PNH patients and inhibits terminal complement mediated intravascular hemolysis. However, eculizumab preserves the early components of complement activation that are essential for opsonization of microorganisms and clearance of immune complexes.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Eculizumab is to be administered via IV infusion over minutes. The proposed eculizumab dosage regimen is as follows:

- 600 mg every 7 days for the first 4 weeks, followed by
- 900 mg for the fifth dose 7 days later, and then
- 900 mg every 14 days thereafter

Eculizumab should be administered at the recommended dosage regimen time points, or within two days of these time points. If a reduction in serum lactic dehydrogenase (LDH) is not achieved following multiple administrations of eculizumab at 14 days intervals, the dosing interval may be reduced to 12 days.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The pivotal trial used to support the dosing of eculizumab or claims in the labeling was Study C04-001 (or TRIUMPH study) conducted in 87 PNH patients. The design features of the trial are shown in the table below:

Study Number	Indication	Design ^a	Duration of Treatment	Dose (mg/kg)	Number of Patients
C04-001	PNH	r, db, pc	26 weeks	A) Placebo B) 600 mg weekly x4 then 900 mg Q2wks	87 patients (43 patients on active treatment)

^a r=randomized, db=double-blind, pc=placebo-controlled, op= open-label

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Severe anemia requiring transfusion is a serious morbidity in PNH, as refractory transfusion-dependent hemolytic anemia is considered a major complication. Hence the co-primary endpoints were hemoglobin stabilization and the number of units of Packed RBCs transfused during the treatment phase of the pivotal trial.

In the clinical trials with PNH patients, two biomarkers for assessing the pharmacodynamics (PD) of eculizumab were evaluated. They are (1) serum hemolytic activity, a measure of terminal complement inhibition in an assay system utilizing antibody-coated chicken RBCs and (2) LDH levels which is an *in vivo* measure of the intravascular hemolysis. Blood samples were collected at Weeks 0 (baseline), 1, 2, 3, 4, 8, 12, 16, 20, 24, and 26 (or early termination whichever comes first) for the measurement of eculizumab concentrations and serum hemolytic activity in Study C04-001. Clinical laboratory tests for LDH were performed at Weeks 0 (baseline), 2, 4, 8, 12, 16, 20, 24, and 26 (or early termination).

2.2.3 Are the active and or relevant moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic and pharmacodynamic parameters and exposure response relationships?

Eculizumab concentrations were determined in serum by a validated enzyme-linked immunosorbent assay (ELISA) method (see 2.6 Analytical section for detailed information). This assay measures total (bound and free) eculizumab concentrations in serum.

2.2.4 Exposure-Response

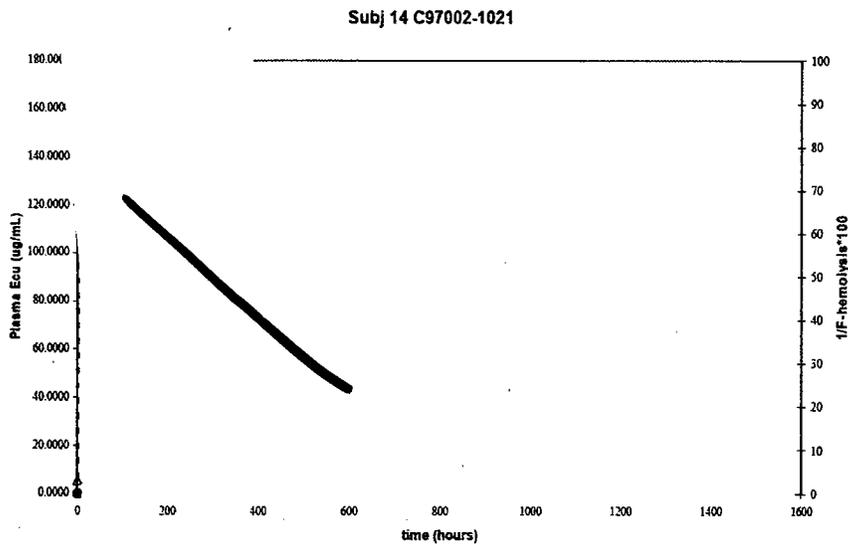
2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The relationship of the eculizumab concentrations with the PD measurement of complement inhibition (*ex vivo* hemolysis) inhibition was explored using maximum PD effect (E_{max}) model. The results of a pooled pharmacokinetic (PK)/PD analysis using data collected from patients with idiopathic membranous glomerulopathy (IMG), rheumatoid arthritis (RA), and PNH are shown in the table below:

Parameter	Estimate	Approx standard error	Lower confidence limit	Upper confidence limit
E _{max}	118.67%	2.691%	114.22%	123.35%
E50	43.2 µg/mL	2.71 µg/mL	39.04 µg/mL	47.78 µg/mL

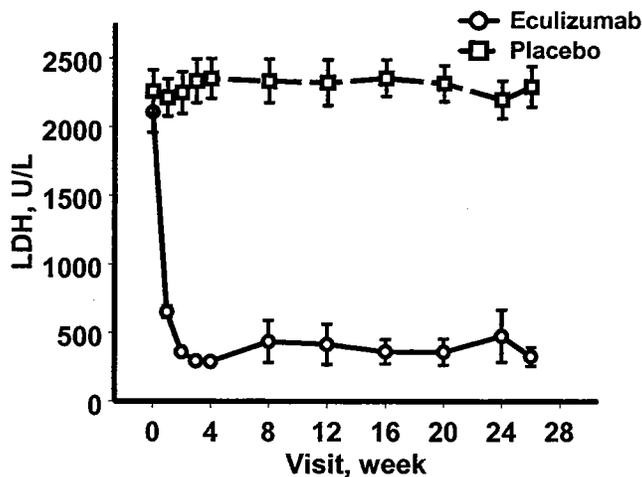
Because the ELISA method used to determine eculizumab concentrations measures both bound and free eculizumab concentrations in human serum, the E50 value of 43 mcg/mL may be an overestimate of eculizumab concentration required to block 50% of maximum terminal

complement activation. The time course and the fit in an example patient are shown in the figure below:



Similar analysis for LDH could not be done as LDH concentration-time profile data following a single dose is not collected. The earliest measurement was performed by Week 1. However, based on the time-course of LDH during the pivotal trial, treatment with eculizumab following the proposed dosing regimen resulted in an immediate (Week 1) and sustained decrease in intravascular hemolysis as evidenced by lowering of LDH levels (Figure 1).

Figure 1: Treatment with eculizumab results in an immediate and sustained lowering of LDH levels



The following table shows the efficacy results from the pivotal study (C04-001):

	Eculizumab (n = 43)	Placebo (n = 44)	P-value
Patients with stabilized hemoglobin levels	49 %	0 %	< 0.01
PRBC units transfused (median, range)	0 (0 - 16)	10 (2 - 21)	< 0.01
Transfusion Avoidance (%)	51 %	0 %	< 0.01
LDH levels at end of study (median)	239 U/L	2,167 U/L	< 0.01
Free hemoglobin at end of study (median)	5 mg/dL	61 mg/dL	< 0.01

* in the pivotal study, 8 patients needed shorter dosing interval from 14 to 12 days to maintain LDH lowering effect

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

Eculizumab was safe and well tolerated. The overall safety profile in eculizumab treated PNH and non-PNH patients were comparable to placebo-treated patients. Hence, no specific analyses were done. The following table shows the safety results (5% or higher in incidence) from Study C04-001.

Adverse Event	Number of Patients (%)	
	Eculizumab Arm (n = 43)	Placebo Arm (n = 44)
Headache	19 (44.2)	12 (27.3)
Nasopharyngitis	10 (23.3)	8 (18.2)
Back pain	8 (18.6)	4 (9.1)
Nausea	7 (16.3)	5 (11.4)
Cough	5 (11.6)	4 (9.1)
Fatigue	5 (11.6)	1 (2.3)
Pruritis	3 (7.0)	3 (6.8)
Constipation	3 (7.0)	2 (4.5)
Respiratory tract infection	3 (7.0)	1 (2.3)
Myalgia	3 (7.0)	1 (2.3)
Pain in extremity	3 (7.0)	1 (2.3)
Herpes simplex	3 (7.0)	0
Sinusitis	3 (7.0)	0

Because the use of eculizumab increases the risk of meningococcal infections, eculizumab labeling will include a black box warning on serious meningococcal infections and a requirement on meningococcal vaccination at least 2 weeks prior to the initiation of eculizumab therapy.

2.2.4.3 Does this drug prolong the QT or QTc interval?

No clinical study has been conducted to determine the effect of eculizumab on QT interval.

2.2.4.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

By Week 1, the mean trough concentration of eculizumab was achieved above 40 mcg/mL in the pivotal trial following the administration of proposed eculizumab dosage regimen and the trough concentrations were sustained at approximately 100 mcg/mL. It was also seen that these levels resulted in immediate (Week 1) and sustained lowering of serum LDH, a marker for intravascular hemolysis (Figure 1). Based on the exploratory PK/PD analysis using an Emax model, the E50 concentration of eculizumab was roughly 43 mcg/mL.

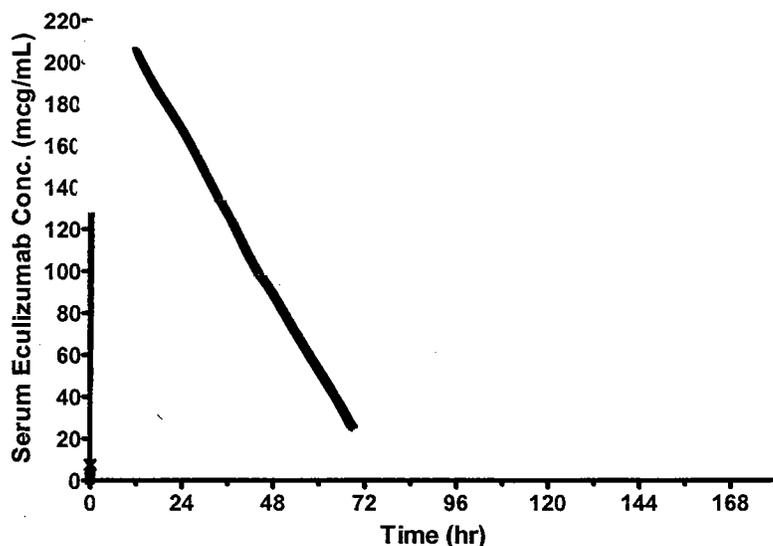
2.2.5 What are the pharmacokinetic characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

Single Intravenous Dose Pharmacokinetics

Single-dose eculizumab PK have not been studied in patients with PNH. When assessed in patients with RA (Study C97-001) and systemic lupus erythematosus (SLE, Study C97-001), eculizumab serum concentrations were consistently detectable following a single 30-min infusion of eculizumab at a single dose of 4 or 8 mg/kg body weight. A striking feature of eculizumab concentration-time curve is the presence of second peak at approximately 2 days post dose (Figure 2). The reason for the second peak is not clearly known.

Figure 2: Eculizumab serum concentration-time profiles determined in patients with rheumatoid arthritis following an intravenous infusion of eculizumab 8 mg/kg over 30 minutes (Study C97-001)



The volume of distribution (Vd) of eculizumab was slightly larger than the serum volume of an adult as expected following an administration of human IgG-type antibody (Table 1). The systemic clearance (CL) of eculizumab was low as expected. The terminal half-life ($t_{1/2}$) was relatively shorter than normal human IgG-type antibodies.

2.2.5.4 *What are the characteristics of drug distribution?*

Eculizumab appears to be distributed mainly intravascularly. The mean volume of distribution determined in patients with PNH (Table 2) is slightly larger than the serum volume of an adult.

2.2.5.5 *Does the mass balance study suggest renal or hepatic as the major route of elimination?*

Not applicable to biologics.

2.2.5.6 *What are the characteristics of drug metabolism?*

Not applicable to biologics.

2.2.5.7 *What are the characteristics of drug excretion?*

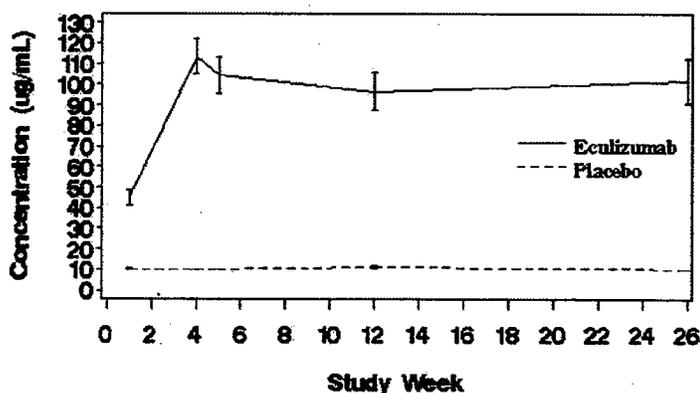
Not applicable to eculizumab.

2.2.5.8 *Based on pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?*

The degree of linearity in dose-concentration relationship cannot be definitely determined. Two fold increase in dose from 4 to 8 mg/kg raised the mean C_{max} values by approximately 60% and 15%, and the mean AUC_∞ values by 70% and 103% in patients with RA and SLE, respectively (Table 1). However, the % increases in C_{max} and AUC values were greatly influenced by the inclusion/exclusion of outliers in the RA study and too small number of patients were evaluated in the SLE study. The dose-linearity has not been determined in PNH patients.

2.2.5.9 *How do the pharmacokinetic parameters change with time following chronic dosing?*

Based on the multiple dose data in PNH patients (Study C04-001), there was no apparent indication of change in the pharmacokinetics over duration of the trial (26 weeks). The mean trough concentrations of eculizumab were similar from Week 5 to Week 26 as shown in the figure below:



2.2.5.10 What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers and patients, and what are the major causes of variability?

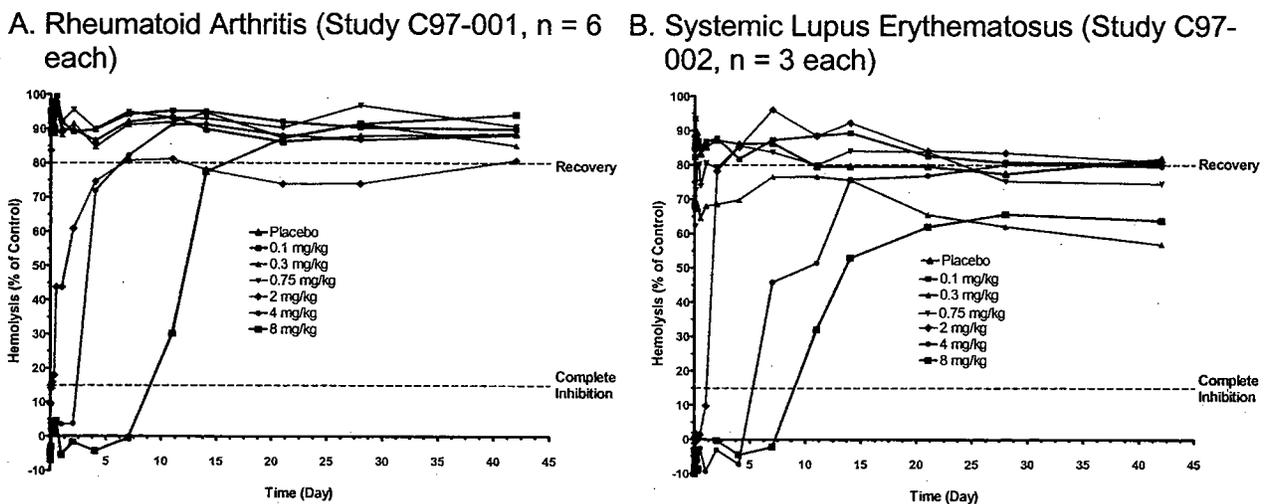
Based on the population analysis of sparse data collected from PNH patients, the between-subject variability in eculizumab clearance was 40%, while that of volume of distribution was 16%. No major prognostic factors explaining the variability were explored in PNH patients.

2.2.6 What are the pharmacodynamic characteristics of the drug? (Include PD parameters that are not addressed in 2.2.4 but important to understand the clinical pharmacology of the drug)

Eculizumab pharmacodynamics were assessed by evaluating the extent and duration of the systemic complement inhibition. Complement activity was assayed using a procedure that measures complement-mediated hemolysis of chicken RBCs sensitized with anti-RBC antibodies (see Section 2.6. Analytical). It is unknown whether this *ex vivo* assay correlates with *in vivo* hemolytic response in patients with PNH.

Figure 3 displays the mean hemolytic activity expressed as percent of control determined in patients with RA and SLE over time following a single eculizumab dose. Complete inhibition appears to be dose-related: the duration of complete inhibition defined as < 15% of baseline value and time to recovery defined as > 80% of baseline were apparently dose-related. Eculizumab doses of 0.75 mg/kg or lower had little effect on total serum hemolytic activity at any time, whereas complete inhibition of hemolytic activity was achieved in almost all patients who received an eculizumab dose of 2.0 mg/kg or higher. The onset of complete inhibition occurred before the first sampling time at 15 minutes after the end of the infusion. Whereas the duration of complete inhibition for the 4.0 mg/kg group in the RA study was approximately 2 days, the duration for the 8.0 mg/kg group ranged from 7 to 14 days. Whereas the recovery time for the 4.0 mg/kg group ranged from 7 to 11 days, the recovery time for the 8.0 mg/kg group ranged from 11 to 21 days. The duration of complete inhibition and recovery time were similar in the SLE study after adjusting the difference in baseline values.

Figure 3: Mean hemolytic activity (% of Control) determined in patients following a single intravenous infusion of eculizumab over 30 minutes.



Eculizumab induced a concentration-dependent inhibition of serum hemolytic activity in patients with RA and SLE. There appears to be an inverse relationship between serum eculizumab concentrations and C5 inhibition. Figure 4 shows the relationship between eculizumab concentration and hemolytic activity expressed as % of control. In patients who achieved complete C5 inhibition, the eculizumab serum concentrations at the last time point before loss of complete inhibition ranged from 29 mcg/mL to 55 mcg/mL in the RA study. The eculizumab serum concentrations associated with the earliest recovery values ranged from 11 mcg/mL to 35 mcg/mL in the SLE study. These ranges are considered to be rough estimates of the concentrations necessary for complete inhibition and recovery. The Sponsor proposes in the

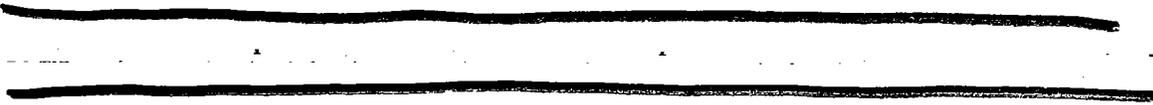
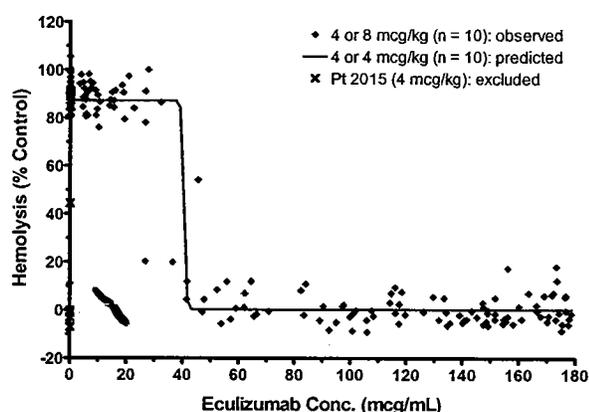
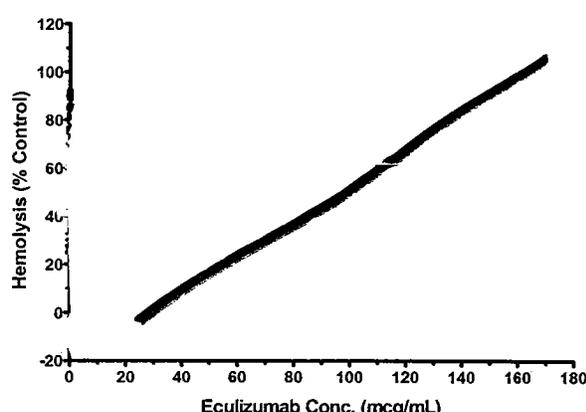


Figure 4: Relationship between eculizumab concentration and hemolytic activity following a single intravenous infusion of eculizumab to patients

A. Rheumatoid Arthritis (Study C97-001)



B. Systemic Lupus Erythematosus (Study C97-002)



2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Based on the population analysis of eculizumab PK and PD (i.e., serum complement inhibition activity), no intrinsic factors (i.e., gender, race, age, height, weight, and estimated creatinine clearance) affecting the PK and PD parameters were identified.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

No specific studies were conducted to evaluate the clinical pharmacology of eculizumab in the elderly. In a population PK analysis, the effect of age on eculizumab PK was not significant. In Study C04-001, 6 out of 43 PNH patients received eculizumab were elderly patients.

2.3.2.2 Pediatric Patients

Not applicable. Pediatric studies were waived for the proposed indication due to orphan drug designation.

2.3.2.3 Gender

No specific studies were conducted to evaluate the effect of gender on the clinical pharmacology of eculizumab. In population PK and PD analyses, the effect of gender on eculizumab PK or PD was not significant. In Study C04-001, 43 PNH patients received eculizumab consisted of 23 females and 20 males.

2.3.2.4 Race

No specific studies were conducted to evaluate the effect of race on the clinical pharmacology of eculizumab. In population PK and PD analyses, the effect of race on eculizumab PK or PD was not significant. In Study C04-001, 37 out of 43 PNH patients received eculizumab were Caucasians.

2.3.2.5 Renal impairment

No specific studies were conducted to evaluate the effect of renal impairment on the clinical pharmacology of eculizumab. In population PK or PD analyses, the effect of estimated creatinine clearance on eculizumab PK or PD was not significant.

2.3.2.6 Hepatic impairment

No specific studies were conducted to evaluate the effect of hepatic impairment on the clinical pharmacology of eculizumab.

2.3.2.7 What pregnancy and lactation use information is there in the application?

Pregnancy Category C: No clinical studies have evaluated Soliris use in pregnant women. Soliris is a recombinant IgG molecule, and IgG molecules are known to cross the placental barrier. Animal reproduction studies have not been conducted with Soliris. In animal reproduction studies that used a surrogate murine anti-C5 antibody of Soliris, developmental abnormalities were observed. Soliris should be used in pregnant women only if clearly needed.

2.3.3 Immunogenicity (applicable only to biologics)

2.3.3.1 Are the anti-drug antibodies in serum (or other biological fluid) appropriately identified and measured to assess immunogenicity? (If yes, refer to Section 2.6, Analytical; if no, describe the reasons.)

No. A partially validated ELISA method was used to detect anti-eculizumab antibodies in human serum samples. The assay method was reviewed in detail in Section 2.6. Analytical section. The assay method may not be able to detect all possible anti-eculizumab antibodies since the assay method used an Fab fragment as the target molecule for detection of anti-eculizumab antibodies.

2.3.3.2 What is the incidence (rate) of the induction of the anti-drug antibodies?

Since eculizumab is a humanized monoclonal antibody, eculizumab may induce human anti-human antibodies (HAHA). The rates of the induction of anti-eculizumab antibodies observed in PNH and non-PNH studies following the treatment of eculizumab or placebo are summarized in the table below:

	PNH		Non-PNH		All Eculizumab Studies	
	Placebo	Eculizumab	Placebo	Eculizumab	Placebo	Eculizumab
Total Patients with HAHA Measurement, n	44	151	206	677	250	828
Patients with a Positive HAHA Response, n (%)	1 (2.3)	2 (1.3)	11 (5.3)	26 (3.8)	12 (4.8)	28 (3.4)
Patients with an IgM Response, n (%)		1 (0.7)	5 (2.4)	7 (1.0)	5 (2.0)	8 (1.0)
Patients with an IgG Response, n (%)	1 (2.3)	1 (0.7)	7 (3.4)	20 (3.0)	8 (3.2)	21 (2.0)
Patients with and IgG and IgM Response, n (%)	-	-	1 (0.5)	1 (0.1)	1 (0.4)	1 (0.1)
Patients with Persistent Response	-	1 (0.7) ²	1 (0.5) ³	1 (0.1) ³	1 (0.4) ³	2 (0.2) ⁴

Apparently, the rates were similar between eculizumab and placebo treatments. In the pivotal PNH study (C04-001), 1 out of 43 (2.3%) eculizumab-treated patients and 1 out of 44 placebo-treated patients demonstrated a detectable HAHA response at the last study visit (Week 26). The single response in the eculizumab cohort was of low titer (1:20), and had no apparent effect on the pharmacokinetics and pharmacodynamics of eculizumab.

However, the immunogenicity study results presented in the table above should be interpreted with caution since almost all serum samples for immunogenicity tests were drawn in multiple dose studies before eculizumab was completely cleared (mostly at troughs). According to the lead CMC reviewer, Dr. Michelle Frazier-Jessen, the degree of interference on immunogenicity assay by residual eculizumab has not been adequately assessed and the assay method used to determine the immunogenicity does not appear to be adequately validated. Therefore, it is possible that low titer antibodies might be missed due to assay interference by eculizumab or other interfering compounds.

2.3.3.3 Do the anti-drug antibodies neutralize the effect of the drug? (If yes, include a neutralization assay method(s) in Section 2.6 Analytical.)

The Sponsor concluded that neutralizing HAHA responses have not been observed with all 911 patients treated with eculizumab for various diseases. There was no concurrent increase in serum LDH levels at the time points where PNH patients exhibited positive HAHA responses. However, the conclusion does not appear to be definitive since no neutralization assay has been performed.

2.3.3.4 Does the immunogenicity affect the PK and/or PD of the drug?

The Sponsor concluded that HAHA induction had no apparent impact on the PK and PD parameters evaluated for eculizumab in PNH patients. However, the conclusion does not appear to be definitive since the sparse PK sampling and a small number of patients with weak immunogenicity response do not allow adequately detecting changes in PK and PD.

2.3.3.5 What is the clinical impact of the induction of anti-drug antibodies on the efficacy and safety?

There appears to be no apparent impact of anti-eculizumab antibody on the efficacy and safety of eculizumab. However, a definitive conclusion cannot be made based on the small number of PNH patients demonstrated immunogenicity to eculizumab and the assay method with insufficient validation.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No specific studies or analyses were conducted to evaluate the effect of the extrinsic factors on the clinical pharmacology of eculizumab.

2.4.2 Drug-drug interactions

No drug-drug interaction studies were conducted using eculizumab. In Study C04-001, all 41 enrolled patients with PNH received the *N meningitidis* vaccine as required by the protocol in addition to eculizumab. Thirty-one (72%) were receiving antianemic preparations such as cyanocobalamin, erythropoietin, various iron preparations, and folic acid. Analgesics, antithrombotic agents, and antibacterials were taken by approximately half to two-thirds of all patients. Systemic corticosteroids were taken by approximately one-third of enrolled patients.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No unresolved issues or omissions related to dose, dosing regimens, or administration are identified in this submission.

2.5 General Biopharmaceutics

This section should summarize the salient points about the attributes of the drug product. (For Biologics, see 2.5.10 only. Others biopharmaceutics questions are not applicable to Biologics.)

2.5.10 What is the pharmacokinetic and/or pharmacodynamic comparability of the proposed to-be-marketed formulation to the pivotal clinical trial? (Applicable to Biologics only)

The eculizumab manufacturing process has undergone a series of modifications. The proposed to-be-marketed drug substance manufacturing process, [REDACTED], was preceded by [REDACTED] processes; [REDACTED]. The pivotal efficacy study C04-001 and the subsequent safety study C04-002 used clinical trial material produced from [REDACTED]. The changes from [REDACTED] include: (1) [REDACTED]
[REDACTED]
[REDACTED]

No pharmacokinetic or pharmacodynamic comparability study was conducted in humans to determine the comparability between Process [REDACTED]. According to the CMC reviewer, Dr. Joseph Kutza, the differences between the [REDACTED] manufacturing processes are not considered to be significant. Thus, a PK or PD comparability study does not appear to be necessary.

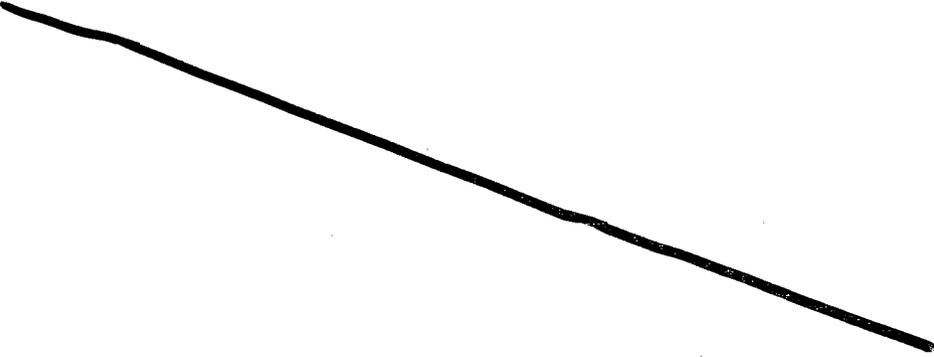
2.6 Analytical

This section should address issues related to the analytical and bioanalytical methods used to support the CPB studies. (For Biologics, see 2.6.5, 2.6.6 and 2.6.7 only. Others analytical questions are not applicable to Biologics.)

2.6.5 What bioanalytical methods were used to assess the concentrations of the drug in serum or other biological fluids?

Enzyme-linked immunosorbent (ELISA) methods were used to determine the total (bound + free) concentrations of eculizumab in human serum samples. In the final validated method: [REDACTED] commercial ELISA plates are coated with purified human C5 (antigen coat). [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

For assay validation, six standard curve samples containing eculizumab at the concentration range from [REDACTED] were used to quantify eculizumab concentrations in QC samples containing known concentrations of eculizumab (20, 120, and 240 mcg/mL). The acceptance criteria for the linearity, accuracy and precision of the assay were coefficient of determination



The stability of QC samples was evaluated over time and at multiple storage conditions. Stability acceptance criteria (accuracy of $100 \pm 25\%$ recovery; precision of $\leq 20\%$ CV) were met for all samples tested under conditions specified in the clinical study protocols. Eculizumab in serum was stable for at least 8 hours at room temperature prior to cold storage.

2.6.5.1 Do the measured concentrations reflect the amount (e.g., immunoassay) or activity (e.g., bioassay) of the drug in biological fluids?

The eculizumab concentrations measured by ELISA methods reflect the amount of the drug in serum.

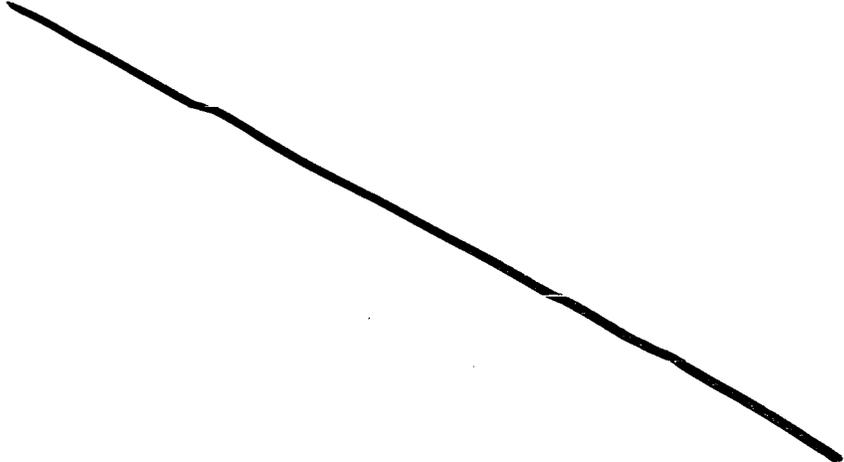
2.6.5.2 What are the limitations, if any, of the concentration values measured by the analytical methods to be used for the pharmacokinetics, pharmacodynamics or clinical assessment of the drug?

In single dose pharmacokinetic studies conducted in patients with RA (C97-001) and SLE (C97-002), the ELISA method of [REDACTED] was initially used and provided inconsistent results with high level of background signal in the pretreatment samples. Therefore, samples from some patients who received high dose eculizumab in the two studies were reanalyzed using 'TM method.' TM method was revised and matured to the final validated method, [REDACTED]

2.6.6 What bioanalytical methods were used to detect anti-drug antibodies in serum or other biological fluids?

A partially validated ELISA method was used to detect anti-eculizumab antibodies in human serum samples. Because there was no anti-eculizumab human plasma or sera available to be used as a positive control for quantifying concentrations of these anti-human antibodies, this assay was not formally validated for accuracy, precision, range, linearity, or limits of detection. The assay method may not detect all possible anti-eculizumab antibodies since the assay method used an Fab fragment as the target molecule for detection of anti-eculizumab antibodies.

In this assay, anti-eculizumab antibodies present in patient serum samples were detected by capture on ELISA plates coated with an Fab fragment of eculizumab. The assay was performed on duplicate plates, which are processed to detect either human IgM or human IgG antibodies bound to the eculizumab Fab fragment. For each patient sample to be assayed, a pretreatment



All assays examined met predetermined acceptance criteria; the mean OD for positive controls was █████ for the IgG positive control and █████ for the IgM positive control. The positive controls for this assay were therefore considered sufficient to monitor assay reagents.

2.6.6.1 What criteria were used to conclude whether the anti-drug antibody production was positive or negative?

A treatment OD value of >3 times the pretreatment value was considered a significant induction in the levels of human-anti-eculizumab antibodies.

2.6.6.2 If the anti-drug antibodies neutralize the effect of the drug, how was the neutralization effect measured?

The anti-eculizumab antibodies are not known to neutralize the effect of eculizumab. The neutralizing assay method has not been developed and the neutralization effect was not measured.

2.6.7 What bioanalytical methods were used to assess the pharmacodynamic effect of the drug?

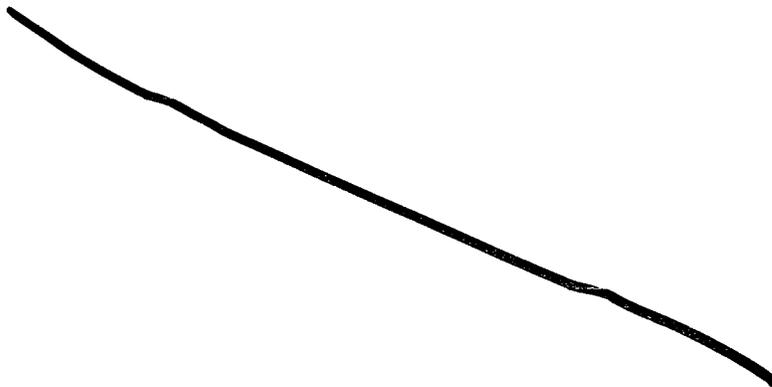
A hemolytic assay was used to determine the biologic activity of eculizumab in human serum samples. This assay measures the hemoglobin release from sensitized RBC due to cell lysis by the terminal complement complex (C5b-9) deposited on the surface of these cells. Results are reported as % baseline hemolysis. Eculizumab binds with high affinity to human serum complement protein C5 and inhibits the production of C5b-9 by blocking C5 cleavage. Therefore, the ability of human serum to lyse sensitized chicken RBCs is inversely proportional to the amount of eculizumab present.

In the final validation of the assay, the standard curve, QC, and patient samples were serially diluted (1:2 ratio) in gelatin veronal-buffered saline (GVB2+) and added in triplicate to a 96-well

plate. The standard curve (concentration range, _____ and QC (concentrations at 2, 10, 30, and 60 mcg/mL) samples were prepared with normal human serum (20% v/v) and reference standard eculizumab. Positive control (normal human serum) and patient samples were diluted such that the final serum concentration in each well is 20% v/v. The erythrocytes were sensitized by addition of an anti-chicken RBC polyclonal antibody. The sensitized erythrocytes were added to the assay plate. After transferring the supernatants to a new plate, hemoglobin release was determined by reading the OD at _____. The percent hemolysis is calculated using the following formula:

$$\% \text{ Hemolysis} = (\text{OD sample} - \text{OD blank}) / (\text{OD positive control} - \text{OD blank}) \times 100.$$

A partial validation was performed for this assay. The LOQ was not evaluated as this type of assay is not quantitative enough to make the evaluation meaningful. The linearity of this assay was also not addressed as the assay response is inherently abrupt and nonlinear. A validation performed on _____ assay plates using the standard curve samples met the acceptance criteria. The validation criteria for accuracy and precision are listed in the table next page.



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 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

4 APPENDICES

4.1 Package Insert (Proposed and Annotated)

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4.2 Summary of Individual Studies

4.2.1 Clinical and Clinical Pharmacology Studies Conducted in Patients with PNH

Study Number	Indication	Design ^a	Duration of Treatment	Dose (mg/kg)	PK/PD	HAHA	Number of Patients Enrolled
C02-001	Paroxysmal Nocturnal Hemoglobinuria	open label pilot study	3 months	600mg Qwk x4, then 900mg Qwk, then 900mg Q2wks	Yes	Yes	11
E02-001	Paroxysmal Nocturnal Hemoglobinuria	open label extension: C02-001	52 weeks	900mg Q2wks	Yes	Yes	11
X03-001 and Addendum	Paroxysmal Nocturnal Hemoglobinuria	open label extension: E02-001	104 weeks	900mg Q2wks	Yes	Yes	11
C04-001	Paroxysmal Nocturnal Hemoglobinuria	r, db, pc Phase III	6 months	Placebo 600mg Qwk x4, then 900mg Qwk, then 900mg Q2wks	Yes	Yes	44 43
C04-002	Paroxysmal Nocturnal Hemoglobinuria	open label	52 weeks	600mg Qwk x4, then 900mg Qwk, then 900mg Q2wks	Yes	Yes	97 ongoing
E05-001	Paroxysmal Nocturnal Hemoglobinuria	open label	104 weeks	600mg Qwk x4; 900mg Qwk; 900mg Q2wks or: 900mg Q2wks	Yes	Yes	96 As of March 2006

^ar, randomized; db, double blind; pc, placebo controlled

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4.2.2 Clinical and Clinical Pharmacology Studies Conducted in Patients with Diseases other than PNH

Study Number	Indication	Design ^a	Duration of Treatment	Dose (mg/kg)	PK/PD	HAHA	Number of Patients Enrolled
C97-001	Rheumatoid Arthritis	r, db, pc Phase I	Single dose	Placebo 0.1mg/kg 0.3mg/kg 0.75mg/kg 2.0mg/kg 4.0mg/kg 8.0mg/kg	Yes	Yes	10 4 4 4 8 6 6
C99-001	Rheumatoid Arthritis	r, db, pc Phase II	12 weeks	A) Placebo B) 8mg/kg Q2wks C) 8mg/kg Qwk x5, then Q4wks D) 8mg/kg Qwk x5, then Q2wks	Yes	Yes	57 61 59 56
E99-001	Rheumatoid Arthritis	open label extension: C99-001	1 year	8mg/kg Q2wks	Yes	Yes	132
C01-004	Rheumatoid Arthritis	r, db, pc Phase IIb	24 weeks	A) Placebo B) 600mg Qwk x5, then Q4wks C) 600mg Qwk x5, then Q2wks	Yes	Yes	108 133 135
E01-004	Rheumatoid Arthritis	r, db, pc. extension: C01-004	1 year	D) 600mg Qwk x5, then Q4wks E) 600mg Qwk x5, then Q2wks F) continuation of C01-004 Group B 600mg Q4wks G) continuation of C01-004 Group C 600mg Q2wks	NA	Yes	254 complete but not unblinded
C97-002-01	Systemic Lupus Erythematosus	r, db, pc. Phase I	Single dose	Placebo 0.1mg/kg 0.3mg/kg 0.75mg/kg 2.0mg/kg 4.0mg/kg 8.0mg/kg	Yes	Yes	6 3 3 3 3 3 3
C99-004	Idiopathic Membranous Glomerulopathy	r, db, pc Phase II	16 weeks	A) Placebo B) 8mg/kg Q4wks C) 8mg/kg Q2wks	Yes	Yes	44 29 49
E99-004	Idiopathic Membranous Glomerulopathy	open label extension: C99-004	12 months	8mg/kg Q2wks	NA	Yes	72
C99-007	Psoriasis	r, db, pc Phase II	8 weeks	A) Placebo B) 8mg/kg Q2wks C) 8mg/kg Qwk x5, then Q2wks	Yes	Yes	10 11 19
C99-006	Dermatomyositis	r, tp, pc pilot study	8 weeks	A) Placebo B) 8mg/kg Qwk x5, then Q2wks	Yes	Yes	3 10

^a r, randomized; db, double blind; pc, placebo controlled

4.3 Consult Reviews

See Attachment

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4.4 OCPB Filing/Review Form

Office of Clinical Pharmacology BLA Filing and Review Form				
General Information About the Submission				
	Information		Information	
Application Number	STN125166/0		Brand Name Soliris	
OCPB Division	OCP5		Generic Name Eculizumab	
Medical Division	DMIHP		Drug Class Biologics, mAb	
OCPB Reviewer	Jang-ik Lee		Indication(s) Treatment of paroxysmal nocturnal hemoglobinuria	
OCPB Team Leader	Hong Zhao		Dosage Form and Strengths Injectable solution, 30 mL/vial (10 mg/mL)	
Date of Submission	9/15/06 (letter)		Dosing Regimen 600 mg q1 wk x 5, 900 mg q1 wk x1, then 900 mg q2 wks	
Estimated Due Date of OCP Review	2/1/07		Route of Administration IV	
PDUFA Due Date	3/17/07		Sponsor Alexion	
Division Due Date	2/6/07		Priority Classification priority review (subpart E)	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			ELISA
I. Clinical Pharmacology				
Mass balance:	NA			Biologics
Isozyme characterization:	NA			Biologics
Blood/plasma ratio:	NA			Biologics
Plasma protein binding:	NA			Biologics
Pharmacokinetics (e.g., Phase I)				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	2 (0 with PNH)	2 (0 with PNH)	C97-001 (RA), C97-002 (SLE)
multiple dose:	X	12 (4 with PNH)	4 (2 with PNH)	Estimated using modeling with sparse sampling: C99-004 (IMG), C01-004 (RA), C02-001 (PNH), C04-001 (PNH)
Dose proportionality -	X	6 in RA and SLE	2	Studied below proposed doses: C97-001 (RA), C97-002 (SLE)
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			E-R analysis to select dose

Phase 3 clinical trial:				
Population Analyses -	X			Compared PK & PD btwn Dz
Data rich:				
Data sparse:	X			
Immunogenicity	X			
II. Biopharmaceutics				
Absolute bioavailability:	NA			IV
Relative bioavailability -	NA			IV
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	NA			IV
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	NA			IV
Dissolution:	NA			IV
(IVIVC):	NA			IV
Bio-wavier request based on BCS	NA			IV
BCS class	NA			IV
Comparability	Not done			Needs in-depth discussion
III. Other CPB Studies				
Genotype/phenotype studies:	Not done			
Chronopharmacokinetics	Not done			
Pediatric development plan	waiver requested			
Literature References	X			
Total Number of Studies All		14 (4 with PNH)	6 (2 with PNH)	
Fitability and QBR comments				
	"X" if yes	Comments		
Application fileable?	Filed	Are the PK parameters estimated using compartmental modeling with sparse sampling acceptable for labeling? If not, as proposed by the Sponsor, will the estimated PK parameter acceptable for now and to be revised after conducting a PK study with a PMC?		
Comments sent to firm?				
QBR questions (key issues to be considered)				
Other comments or information not included above	Orphan Drug Designation Granted, Fast Track refused, Priority Review to be granted (subpart E, treatment of thromboembolism)			
Primary reviewer Signature and Date	Jang-ik Lee			
PM reviewer Signature and Date				
Secondary reviewer Signature and Date	Hong Zhao			

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