CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	BB 125166/0
Drug Name:	Eculizumab
Indication(s):	Paroxysmal Nocturnal Hemoglobinuria
Applicant:	Alexion
Date(s):	Date submitted: September 15, 2006
	PDUFA due date: March 16, 2007
	Review completion date: February 01, 2007
Review Priority:	Priority
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Keywords: paroxysmal nocturnal hemoglobinuria, eculizumab, PNH,

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1. EXECUTIVE SUMMARY

BLA 125166/0 is the original submission for the indication of using eculizumab in the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH). The efficacy results obtained from one Phase III pivotal study were included in the submission as documents for Agency review.

1.1 Conclusions and Recommendations

Based upon the efficacy results presented by the sponsor and this reviewer's statistical evaluation, BLA 125166/0 has demonstrated significant drug effect of using eculizumab in the treatment of patients with paroxysmal nocturnal hemoglobinuria to reduce the need for red blood cell transfusion and to stabilize hemoglobin concentrations. The efficacy results support the indication claim.

1.2 Brief Overview of Clinical Studies

Study C04-001 was the Phase III pivotal clinical trial included in the submission. It was a randomized, double blind, placebo-controlled study using eculizumab administered intravenously in the treatment of patients with paroxysmal nocturnal hemoglobinuria. A total of 87 valid patients were randomized to either placebo or eculizumab group in a 1:1 ratio. All patients received up to 26 weeks of treatment with 16 infusions.

The placebo patients received 1 dose of placebo once a week for 5 weeks, then 1 dose every 2 weeks for 21 weeks. The patients of the eculizumab group received 600 mg of eculizumab once every week for 4 weeks, followed by 900 mg of eculizumab 1 week later for 1 dose, then 900 mg of eculizumab every 2 weeks for 21 weeks. The study period was from August 27, 2004 to December 27, 2005.

The two co-primary efficacy endpoints were hemoglobin stabilization and number of PRBC units transfused. The secondary efficacy variables included transfusion avoidance, hemolysis reduction as measured by LDH area under the curve (AUC), and changes in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale.

The objective of **Study C004-002** was to evaluate the safety of eculizumab in patients with transfusion-dependent hemolytic PNH. The interim report for Study C04-002 included the information from the first patient to the last enrolled patient completed the first 6 months of participation on March 21, 2006.

The primary efficacy endpoint of Study C04-002 was hemolysis as measured by LDH AUC. Secondary endpoints included levels of fatigue as measured by FACIT-Fatigue scale. Exploratory endpoints were LDH change from Baseline, QoL measurements using the EORTC QLQ-C30 instrument, thrombosis, platelet activity, and NO and free hemoglobin measurements.

Two populations were analyzed for this study, the per-protocol (PP) population and the safety population. PP population consisted of all patients who received any amount of eculizumab and had no major protocol violations. A total of 97 patients were included in the PP population. Only one patient discontinued study before Visit 17.

Since Study C04-002 was an open-label trial to evaluate the safety of eculizumab in PNH patients, this review report primarily focuses on drug efficacy in Study C04-001.

1.3 Statistical Issues and Findings

1. A total of 88 patients were randomized. The patients with ID of 027-001 who was not eligible for the study but was randomized to eculizumab group by inappropriately entering into IVRS system. This patient never received any study treatment. It is acceptable to exclude this patient from the intent-to-treat (ITT) population. Therefore, the total N of the ITT population was 87.

   A total of 23 patients were enrolled from sites in Northern America. Among those 23 patients, only one patient (placebo, ID = 061-002) came from Canada and the others were from the US. Forty-four percent (4/9) of the US eculizumab patients were hemoglobin stabilized during the 26 treatment period. In contrast, 51.7% (15/29) of the European eculizumab patients and 50.0% (2/4) Australian eculizumab patients maintained hemoglobin stabilization. In addition, 52.2% (12/23) of female patients and 45.0% (9/20) of male patients in eculizumab group maintained hemoglobin stabilization during the 26 treatment period. Fisher's exact test was used to obtain the p-values.

   Table 1 Summary of Hemoglobin Stabilization , by Region and By Gender

Hemoglobin Stabilization	Eculizumab	Placebo	p-value
US	44.4% (4/9)	0.0% (0/13)	0.0344
Europe	51.7% (15/29)	0.0% (0/27)	<0.0001
Australia	50.0% (2/2)	0.0% (0/4)	0.4286
Female	52.2% (12/23)	0.0% (0/15)	<0.001
Male	45.0% (9/20)	0.0% (0/29)	<0.001

2. The number of PRBC transfusions by region and by gender can be found in Table 2. The results were fairly robust with the US and the other two regions. The mean units of PRBC transfusions for the US patients were 9.9 ± 1.9 units and 4.5 ± 1.8 units for placebo and eculizumab groups, respectively (P = 0.0284). Similarly, the mean units of PRBC transfusions for the female patients were 10.2 ± 0.9 units and 3.3 ± 1.0 units for placebo and eculizumab groups, respectively (P < 0.0001); and the mean units of PRBC transfusions for the males were 12.4 ± 1.6 units and 2.8 ± 0.9 units for placebo and eculizumab groups, respectively (P < 0.0001). The Wilcoxon's rank sum test was used for the comparisons.

Table 2 Mean (SD) Units of Packed Red Blood Cell Transfused from Baseline to Week 26, by Region and By Gender

Mean Units of PRBC Transfused	Eculizumab	Placebo	p-value
US	4.5 (1.84)	9.9 (1.85)	0.0284
Europe	2.8 (0.75)	11.3(0.98)	<0.0001
Australia	1.0 (0.58)	13.3 (3.35)	0.0370
Female	3.3 (1.00)	10.2 (0.94)	<0.001
Male	2.8 (0.88)	12.4 (1.63)	<0.001

Note: The sample size for each of the subgroups is listed in Table 1.

3. The sponsor planned using Fisher's exact test to analyze the exploratory endpoint of thrombosis event. It turned out that only one placebo patient and none of eculizumab patient reported the portal vein thrombosis. However, the sponsor [redacted] Studies C04-001, C04-002, C02-001 and E05-001. Among those four studies, C04-001 was a Phase III, pivotal trial and C04-002 is an on-going, open-label trial to evaluate safety. Thrombosis event was defined as an exploratory endpoint in the protocols of the two studies. [redacted] The plan of [redacted]

4. Similarly, quality of life was an exploratory endpoint defined in the protocol of Study C04-001. It was measured by using EORTC QLQ-C30 instrument, which has not [redacted]

5. In the analysis of FACIT-Fatigue scores, three patients, 013-002, 160-001 and 160-002, were excluded form the mixed model analysis due to missing their baseline FACIT-Fatigue scores. The baseline score was defined as the score collected at Visit 3. If Visit 3 score was missing, the average of Visit 2 would be used as baseline. However, the three patients had no FACIT scores before Visit 4 at all. All of them were placebo patients. This reviewer ran mixed model analysis with imputing their baseline score by the first FACIT score during the treatment period. It was assumed that the three placebo patients had no deteriorated FACIT scores from baseline to the visit of a valid FACIT score collected. The analysis result provided with a p-value of <0.0001 for change of FACIT-Fatigue between baseline and Week 26 (Visit 18). It showed the FACIT-fatigue finding from mixed model is robust when accounting for the missing data.

2. INTRODUCTION

2.1 Overview

Paroxysmal nocturnal hemoglobinuria is an acquired and chronic hemolytic anemia that results from the somatic mutation of the phosphatidylinositol glycan complementation class A (PIG-A) gene in a pluripotent hematopoietic stem cell and the subsequent expansion of an abnormal clone that does not express proteins normally attached to the cell via a glycosylphosphatidylinositol (GPI)-linked protein anchor. The three cardinal features of PNH are hemolysis, cytopenias and thrombosis. More than 80% of hemolytic PNH have prominent hemoglobinuria at some point in the disease.

Eculizumab is a humanized monoclonal antibody that inhibits terminal complement. This inhibition by eculizumab not only prevents the formation of the membrane attack complex but also prevents the release of the proinflammatory mediator C5a.

Study C04-001 was a randomized, double-blind, placebo-controlled, multicenter study of eculizumab or placebo administered intravenously to patients with PNH. Randomized patients received either placebo or eculizumab (600 mg and 900 mg) for a total of 26 weeks of treatment. Each patient who completed the study received 16 infusions (Visits 3-18).

The study included three phases: Enrollment phase (observation period), treatment phase and post-treatment (follow-up) Phase. During the enrollment phase (Visits 1 and 2) up to 3 months, various clinical laboratory tests and vital sign measurements were performed after patients signed up informed consent form. To qualify for this study, the patient must have had a transfusion during the observation period. The hemoglobin set point was determined for each of qualified patients. If no qualifying transfusion was administered during this time period, the patient was considered a screen failure and was not eligible to enter treatment phase. Randomization took place within 10 days of the qualifying transfusion in the observation period.

The treatment Phase included a 5-week induction period (Visits 3-7) and a 21-week maintenance period (Visits 8-18). During the induction period, patients received either eculizumab or placebo each week. Transfusion and thrombosis records were updated, and the patient was to receive 600 mg of study drug at Visits 3-6. At Visit 7, the dose was increased to 900 mg. In the maintenance period, all doses, following the 900 mg dose, occurred at 2-week intervals until Visit 18.

The post-treatment Phase was to monitor patients who discontinued study drug for 8 weeks to ensure the safety and to collect additional study information.

Efficacy Endpoints: The two co-primary efficacy endpoints for this study were hemoglobin stabilization and the number of PRBC units transfused during the treatment phase of the study.

The secondary efficacy endpoints were transfusion avoidance, hemolysis as measured by LDH AUC, and levels of fatigue as measured by the FACIT-Fatigue instrument.

Exploratory endpoints are LDH change from Baseline to Visit 18, Quality of Life (QoL) changes as measured by the EORTC QLQ-C30 instrument, thrombosis rate, platelet activity, and NO and free hemoglobin measures.

2.2 Data Sources

The sponsor provided data electronically. All of the data can be located through the path of \\Cbsap58\M\eCTD_Submissions\STN125166\125166.enx. The folder included all datasets was \Study ID: ISE – STF – ISE\Individual Subjects Data Listing\Analysis data sets\Analysis dataset. All variables of each dataset were well-defined and documented.

3. STATISTICAL EVALUATION

This report includes the detailed statistical review of the pivotal Study C04-001.

3.1 Evaluation of Efficacy

3.1.1 Primary Efficacy endpoints

The two co-primary efficacy endpoints were hemoglobin stabilization and the number of PRBC units transfused during the treatment phase of the study.

To measure patient's hemoglobin stabilization, a hemoglobin set point was pre-determined at the time of the qualifying transfusion in the observation period. Hemoglobin stabilization was defined as patient's hemoglobin levels remained above patient's predetermined hemoglobin set point and the patient did not receive a transfusion in the treatment phase.

To qualify for this study, the patient must have had a transfusion during the observation period. The transfusion must have occurred when the patient's hemoglobin value was 9.0 g/dL or lower with symptoms or when the hemoglobin level was 7.0 g/dL or lower without symptoms. Patient's hemoglobin set point was determined after a transfusion during observation period.

For the number of units of PRBC transfused, each patient's units of PRBC transfused after randomization to 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. For patients who had at least 1 transfusion, but withdrew prematurely from the study prior to 26 weeks, the number of units was adjusted by the number of weeks on study drug during the treatment period, i.e., the adjusted units of PRBC transfused = (26/number of weeks on study drug) × (number of units transfused while on study drug).

Determination of Sample Size: Assuming incidence rates of hemoglobin stabilization were [redacted] for the placebo and eculizumab groups, respectively and the median units of transfusion during the treatment phase were [redacted] for the placebo and eculizumab groups, respectively, the study sample size of 75 patients was estimated for approximately [redacted] power, using the 2-sided Fisher exact test for hemoglobin stabilization and the Wilcoxon's rank sum test for units of PRB transfused.

Randomization Study: All the patients were randomly assigned in a 1:1 ratio to placebo or eculizumab by a centralized allocation method. Randomization took place within 10 days of the qualifying transfusion in the observation period. Randomization was stratified according to the number of PRBC units transfused within 1 year prior to screening. The 3 randomization strata used were between 4 and 14 units, between 15 and 25 units, and greater than 25 units.

3.1.2 Secondary Efficacy Endpoints

Transfusion avoidance: The occurrence of PRBC's transfusion during the treatment phase
Area Under the Curve of Lactate Dehydrogenase: A quantitative assessment of chronic hemolysis obtained by calculating the AUC for LDH from baseline to Week 26
Levels of fatigue: Measured by the FACIT-Fatigue instrument and used the scoring guidance for the FACIT-Fatigue instrument to calculate a fatigue score

3.1.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

A total of 109 subjects enrolled into the study and 1 did not meet enrollment criteria. Among the 108 patients who entered observation period; 88 patients were randomized; 87 entered treatment phase; 2 patients terminated early; 10 placebo patients discontinued treatments due to lack of efficacy but completed all visits; and 75 completed the treatment phase as scheduled.

Demographic and Other Baseline Characteristics

Demographics and baseline characteristics (ITT population) are summarized in Table 3 for placebo and treatment group. The mean ages of patients of eculizumab and placebo groups were 42.1 ± 15.5 years and 38.4 ± 13.4 years, respectively. Males and females were evenly distributed in placebo and treatment group. Excluding those patients of France sites because local law in France did not allow the collection of race information, the majority of patients were Caucasians (86.0% of eculizumab patients and 93.2% of placebo patients). There were no statistically significant differences between the two groups at baseline for all demographic variables in Table 3. Most patients were under age 65 (86% of eculizumab patients and 95.5% of placebo patients).

The mean hemoglobin set points between placebo and eculizumab group were not similar (See Table 3). Based on transfusion histories for all patients, which were collected by the investiators from hospital charts and transfusion unit records, the mean hemoglobin prior to transfusion were 8.0 ± 0.86 g/dL and 7.9 ± 1.02 g/dL for eculizumab and placebo groups, respectively. The mean hemoglobin post transfusion were [redacted] for eculizumab and placebo groups, respectively. The numbers of units

transfused were [redacted] units for eculizumab and placebo groups, respectively. The number of units transfused before randomization, the mean hemoglobin levels prior to transfusion, and post-transfusion were similar between two treatment groups. Chi-square test was used to obtain the p–values in Table 3.

Table 3 Demographics and Baseline Characteristics

	Study C04-001		
	Eculizumab (N=43)	Placebo (N=44)	p-value
Gender			
Male	20 (46.5%)	15 (34.1%)	0.278
Female	23 (53.5%)	29 (65.9%)	
Race			
Caucasian	37 (86.0%)	41 (93.2%)	0.821
Black	4 (9.3%)	0 (0.0%)	
Asian	1 (2.3%)	1 (2.3%)	
Other	0 (0.0%)	1 (2.3%)	
Country			
US/Canada[$]	10 (23.3%)	13 (29.5%)	0.798
Europe	29 (67.4%)	27 (61.4%)	
Australia	4 (9.3%)	4 (9.1%)	
Age			
< 65	37 (86.0%)	42 (95.5%)	0.209
65-75	5 (11.6%)	1 (2.3%)	
≥ 75	1 (2.39%)	1 (2.3%)	
Age			
Mean ± SD	42.1±15.5	38.4±13.4	0.271
Median (Range)	41 (20-85)	35 (18-78)	
Body Weight (kg)			
Mean ± SD	74.9±11.7	72.8±14.0	0.229
Median (Range)	76.1 (53.1-120)	70.0 (61.5-79.6)	
Hemoglobin Set Point			
Mean ± SD	7.8±0.79	7.7±0.75	0.753
Median (Range)	7.7 (6.1-8.8)	7.7 (6.2-9.0)	

Note: $ indicates only 1 placebo patient from Canada in the US/Canada category

3.1.4 Statistical Methodologies

The primary analysis was to focus on the intent-to-treat (ITT) population, defined as all randomized patients. The per-protocol population consists of ITT patients who received any amount of study drug and have no major protocol violations. There was only one patient difference between Per-Protocol population and ITT population. The per-protocol analyses were ignored. The safety population was defined as any patient who received any study drug was considered evaluable for safety analyses.

All analyses for the co-primary efficacy endpoints and the secondary efficacy endpoints were based on the ITT population. All statistical tests were to be two-sided at $\alpha = 0.05$.

Primary Efficacy Analyses
Hemoglobin stabilization was analyzed by using a 2-sided Fisher's exact test. Those patients who withdrew prematurely from the study or were transfused above their hemoglobin set point during the treatment phase also were treated as not achieving hemoglobin stabilization.

The Wilcoxon's rank sum test was used to analyze the number of units of PRBC transfused. 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 PRBCs transfused.

Sensitivity analysis for primary efficacy endpoints
Worst scenario cases analysis was performed as a sensitivity analysis. 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.

The sensitivity analysis for the units of PRBC transfused was planned as following: For each treatment group, available PRBC transfusion unit values were used to impute missing using multiple imputation, mean values, and median values.

Secondary Efficacy Analyses
Transfusion Avoidance was classified for each patient during the 26-week treatment phase by utilizing patients' transfusion records from randomization to Visit 18. Those patients who withdrew prematurely from the study during the treatment phase were treated as requiring transfusion.

AUC of Lactate Dehydrogenase from Baseline to 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 Wilcoxon's rank sum test.

FACIT-Fatigue Scale was analyzed using a mixed-effects model with Baseline as covariate, treatment and time as fixed effects, and patient as random effect. The main hypothesis of interest was that eculizumab will provide a statistically significant increase in patients' total FACIT-Fatigue scale score. Because missing data may not be random, total FACIT-Fatigue scale data also were analyzed by a missing data pattern using the overall patient population and the results are summarized. Treatment effect was examined between the 2 treatment groups within each data pattern.

Analysis of Exploratory Endpoints
Change of LDH from Baseline, EORTC QLQ-C30, Platelet Activity and Nitric Oxide/Free Hemoglobin Measurements were analyzed using a mixed-effects model with treatment and time as fixed effects, and patient as a random effect. Those were exploratory analyses. For each type of event and for the total group of events collected in the thrombosis CRF, the incidence rate is tabulated by treatment group and was analyzed using the Fisher's exact test.

Analysis of Safety Data
Safety was assessed by examination of treatment-emergent adverse events, clinical laboratory results, ECG data, and vital sign measurements collected during the treatment phase and post-treatment phase.

3.1.5 Results and Conclusions

Primary efficacy results were presented for the two co-primary efficacy endpoints separately. Efficacy results for both two co-primary efficacy endpoints demonstrated the statistical significance favoring eculizumab, overall and by subgroup of historical transfusion stratification.

Table 4 shows that overall, 21 (48.8%) of 43 eculizumab patients achieved hemoglobin stabilization compared with 0 (0.0%) of 44 placebo patients ($P<0.001$).

The percentage of eculizumab patients who achieved hemoglobin stabilization was also analyzed by historical transfusion stratification. Hemoglobin stabilization was achieved in the low (4-14 units), mid (15-25 units), and high (> 25 units) strata with 80.0% (12/15 patients), 29.4% (5/17 patients), and 36.4% (4/11 patients) of eculizumab patients demonstrating stabilization, respectively. No placebo patients in any of the randomization strata achieved hemoglobin stabilization. Statistical significance was reached in eculizumab patients in 2 of the 3 strata.

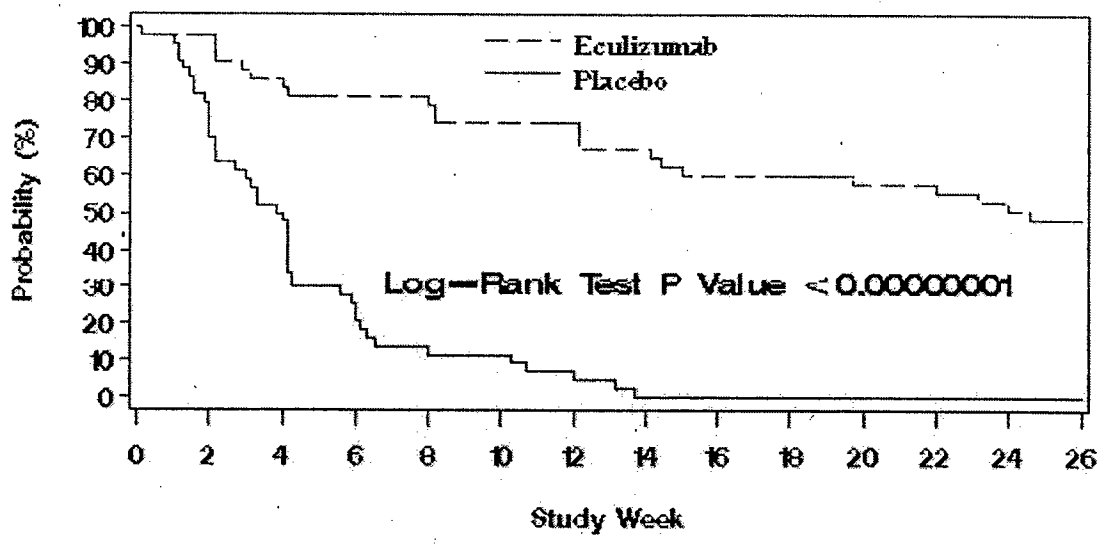
Results from the sensitivity analysis are presented in Table 4 and show a statistically significant level of hemoglobin stabilization in the overall eculizumab treated group relative to placebo ($P<0.001$).

The time to hemoglobin stabilization failure for the 2 treatment groups was analyzed using Kaplan-Meier estimation. The plot illustrates the time to hemoglobin stabilization failure during the study. A log-rank test of these data indicates that the probability of achieving hemoglobin stabilization is statistically significant ($P<0.001$) favoring eculizumab. Figure 1 shows the plot of time to hemoglobin stabilization failure during the study.

Table 4 Hemoglobin Stabilization, Overall and by Baseline Transfusion

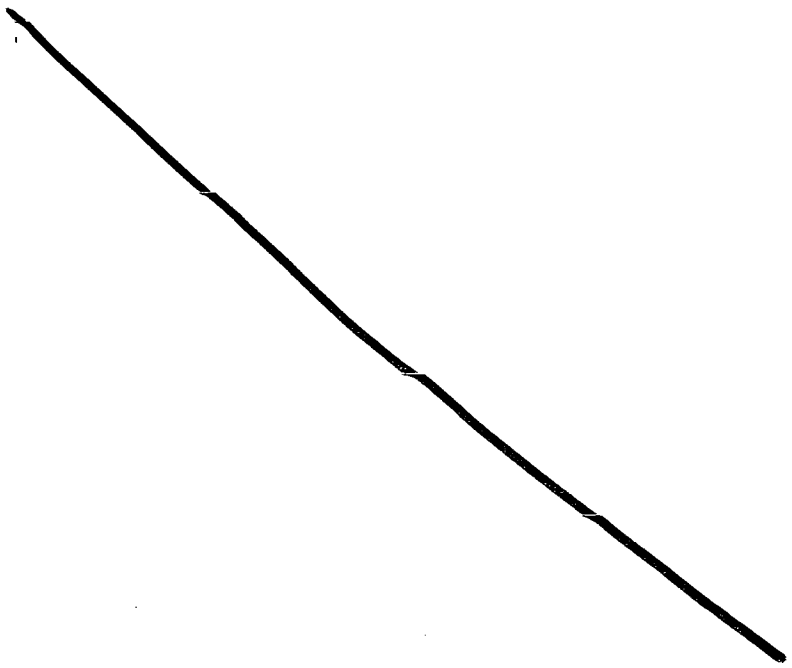
Hemoglobin stabilization	Eculizumab	Placebo	p-value
Overall			
Yes	21 (48.8%)	0 (0.00%)	<0.0001
No	22 (51.2%)	44 (100.0%)	
4-14 units			
Yes	12 (80.0%)	0 (0.00%)	<0.0001
No	3 (20.0%)	15 (100.0%)	
15-25 units			
Yes	5 (29.4%)	0 (0.00%)	0.019
No	12 (70.6%)	18 (100.0%)	
>25 units			
Yes	4 (36.4%)	0 (0.00%)	0.090
No	7 (63.6%)	11 (100.0%)	
Sensitivity analysis			
Yes	21 (48.8%)	5 (0.00%)	<0.001
No	22 (51.2%)	39 (100.0%)	

Figure 1 Time to Hemoglobin Stabilization Failure, by Treatment Group



For the co-primary efficacy endpoint, the units of PRBC transfused during the treatment phase, Table 5 shows eculizumab patients had significant less mean units of PRBC transfused from baseline to week 26. The mean units of PRBC transfused during the treatment phase were [redacted] units for eculizumab and placebo groups, respectively. The difference between the two groups was significant ($P < 0.0001$). Table 5 also shows the mean units of PRBC transfused by historical transfusion strata. The between-group differences were statistically significant for all three strata.

A sensitivity analysis was performed with using mean values and median values to impute missing units of PRBC transfused. The sensitivity analysis provided with the robust results of mean units of PRBC transfused from baseline to Week 26 of [redacted] and [redacted] units for eculizumab and placebo group, respectively ($P < 0.0001$).



Secondary Efficacy Results

Transfusion Avoidance: Overall, [redacted] of eculizumab patients, and none of the placebo patients achieved transfusion avoidance (P<0.001). It was also analyzed by transfusion stratification. Table 6 shows the percentage of patients achieved transfusion avoidance in eculizumab and placebo groups. No placebo patients avoided transfusions in any of the transfusion strata.

Table 6 Summary of Patients Who Avoided Transfusion

Avoid Transfusion	Eculizumab (N=43)	Placebo (N=44)	p-value
Overall	22/43 (51.2%)	0/44 (0.0%)	<0.0001
Baseline 4-14 units	12/15 (80.0%)	0/15 (0.0%)	<0.0001
Baseline 15-25 units	6/17 (35.5%)	0/18 (0.0%)	0.007
Baseline >25 units	4/11 (36.4%)	0/11 (0.0%)	0.09

Area under the Curve of Lactate Dehydrogenase: Differences in LDH AUC values were statistically significantly (P<0.001) different between treatment groups. The LDH AUC was also analyzed by historical transfusion stratification. Statistically significant reductions favoring eculizumab were achieved in all 3 strata.

Table 7 Area under the Curve for Lactate Dehydrogenase

AUC for LDH	Eculizumab (N=43)	Placebo (N=44)	p-value
Overall	81140 ± 17626	429874 ± 21740	<0.0001
Baseline 4-14 units	103760 ± 49309	391386 ± 32020	<0.0001
Baseline 15-25 units	58670 ± 3364	444075 ± 37340	<0.001
Baseline >25 units	85019 ± 16790	459115 ± 44197	0.0001

FACIT-Fatigue: Eculizumab patients demonstrated statistically significant improvements in fatigue levels compared with placebo by Visit 6 (3 weeks after starting treatment) and at subsequent Visits 11, 15, and 18 (Weeks 12, 20, and 26, respectively) (P < 0.01 for all visits, using a Wilcoxon's rank sum test).

Table 8 Change of FACIT-Fatigue Scale Score from Baseline

	Eculizumab (N=43)	Placebo (N=44)	p-value
Baseline	36.7 ± 1.60	34.3 ± 1.88	0.412
Week 3	4.2 ± 1.13	-1.9 ± 1.90	0.009
Week12	4.6 ± 1.22	-3.1 ± 1.52	0.0002
Week 20	4.8 ± 1.56	-2.2 ± 1.91	0.0108
Week 26	6.4 ± 1.19	-4.0 ± 1.71	<0.0001

Exploratory Endpoint – Thrombosis: A portal vein thrombosis was the only MAVE reported among all treated patients. Only 1 placebo patient reported this MAVE. Given the low number of events, a statistical analysis was not performed.

3.2 Evaluation of Safety

The evaluation of safety can be seen in the medical reviewer's report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The two co-primary efficacy endpoints were analyzed by gender subgroup. It was mentioned previously that [redacted] of female patients and [redacted] of male patients in eculizumab group maintained hemoglobin stabilization during the 26 treatment period.

The mean units of PRBC transfused for the female patients were [redacted] ± 1.0 units for placebo and eculizumab groups, respectively ($p < 0.0001$); and the mean units of PRBC transfusions for the males were [redacted] units for placebo and eculizumab groups, respectively ($p < 0.0001$) (see page 4).

4.2 Other Special/Subgroup Populations

[redacted] of the US eculizumab patients were hemoglobin stabilized during the 26 treatment period. In contrast, [redacted]) of the European eculizumab patients and [redacted] Australian eculizumab patients were success in hemoglobin stabilization. No placebo patients achieved hemoglobin stabilization. Table 2 (see page 4) shows the mean unit of PRBC transfused was compared by region subgroup.

There were no multiplicity issues because both two co-primary efficacy endpoints were statistically significant with $p < 0.0001$. No interim analysis was performed during the study ongoing time period. No blinding issues were reported in the submission.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The results from analyzing the two co-primary endpoints had shown the significant treatment efficacy. Subgroup analyses presented robust results as well. The results from analyzing the three secondary efficacy endpoints provided with supportive evidence of treatment efficacy. Study C04-001 was the first clinical trial in the history using experimental drug to assess the efficacy in the treatment of patients with PNH.

Results from the exploratory analyses on thrombosis thromboemolic event [redacted] None of studies that included in this BLA submission were designed to assess the relationship between [redacted] thromboemolic event.

Quality of life was also defined as an exploratory endpoint in the protocol. The instrument of EORTC QLQ-C30 instrument of which was used to measure QoL in C04-001 has never been validated for the PNH patient population. Therefore, [redacted]

5.2 Conclusions and Recommendations

Based upon the consistent efficacy results from the primary and the secondary efficacy analyses, and results from several subgroup analyses, this BLA application has demonstrated significant efficacy of using eculizumab in the treatment of patients with paroxysmal nocturnal hemoglobinuria to reduce the need for red blood cell transfusion and to stabilize hemoglobin concentrations.

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