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APPLICATION NUMBER:

125166

PHARMACOMETRICS REVIEW

Eculizumab (Soliris®)

Pharmacometrics Review

BLA; STN	125166/0000
Submission Date(s)	9/15/06
PDUFA Due Date	3/17/07
Brand Name	Soliris®
Generic Name	Eculizumab
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Sponsor	Alexion Pharmaceuticals
Relevant IND(s)	BB-IND
Submission Type	Original BLA (NME)
Formulation	Solution for intravenous infusion
Proposed indication	Treatment of paroxysmal nocturnal hemoglobinuria
Proposed Dosage and Administration	600 mg qwk x4, 900 mg qwk x1, then 900 mg q2wk

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Executive Summary

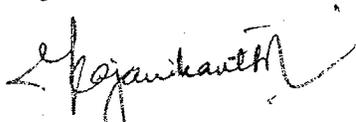
Eculizumab is a humanized monoclonal antibody that binds to the human C5 complement protein and inhibits terminal complement-mediated activation. In the present submission, the sponsor is seeking for the approval of eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), an acquired genetic deficiency of endogenous complement inhibitors on the surface of blood cells.

In the present submission, the sponsor has used pharmacokinetic modeling to derive the pharmacokinetic parameters from the sparse trough and peak serum concentration data collected in the pivotal trial. Relationship between eculizumab activity as assessed by a serum complement hemolysis assay and eculizumab concentrations has also been evaluated using direct PK/PD model.

The summary of the review is:

- 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 \pm SD).
- 2) The mean observed peak and trough serum concentrations of eculizumab by week 26 were 194 ± 76 μ g/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 μ g/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.

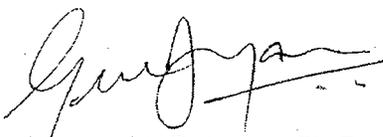
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Introduction

Eculizumab is a humanized monoclonal antibody that binds to the human C5 complement protein and inhibits terminal complement-mediated cell lysis and activation. In the present submission, the sponsor is seeking for the approval of eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).

PNH is an acquired genetic deficiency of endogenous complement inhibitors on the surface of blood cells, referred to as PNH cells. The pathophysiology of PNH is directly linked to complement-mediated destruction of the susceptible PNH red blood cells (RBCs), which result in intravascular hemolysis, the primary clinical manifestation in all PNH patients and contributes to mortality in these patients.

A single phase 3, double-blind, placebo-controlled, comparative pivotal clinical trial (C4-001, n=87) combined with a phase 3 open-label safety and efficacy trial (C04-002, n=97) form the basis of the present marketing application. Additional support for the efficacy and safety of eculizumab as a treatment for PNH patients is provided in the associated PNH extension trial (E05-001).

The primary objective of the pivotal trial (C4-001) was to evaluate the safety and efficacy of eculizumab in patients with transfusion-dependent hemolytic PNH. This trial was a randomized, double-blind, placebo-controlled, multicenter study of eculizumab or placebo administered by intravenous (IV) infusion to 87 patients with hemolytic, transfusion-dependent PNH. Randomization was stratified according to the number of packed red blood cell (PRBC) units transfused within 1 year prior to Screening. Patients randomly assigned to the placebo group received 1 dose of IV placebo weekly for 5 weeks, then once every 2 weeks for 21 weeks for a total of 26 weeks of treatment. Patients randomly assigned to the eculizumab group received 600 mg of eculizumab IV once a week for 4 doses, followed by 900 mg eculizumab IV 1 week later for 1 dose, then 900 mg eculizumab IV every 2 weeks for 21 weeks. There was a total of 26 weeks of treatment. The co-primary endpoints were hemoglobin stabilization and number of PRBC units transfused. For the hemoglobin stabilization endpoint, a 2-sided Fisher exact test was performed. For the number of units of PRBCs transfused, each patient's units of PRBCs transfused after randomization to Week 26 (Visit 18) were calculated and the primary analysis method applied was the Wilcoxon rank sum test. Secondary objectives were transfusion avoidance, hemolysis as measured by lactate dehydrogenase (LDH) area under the curve (AUC) during the treatment period from Baseline to week 26, and Functional Assessment of Chronic Illness Therapy fatigue (FACIT-Fatigue) scale changes from Baseline to week 26.

The pharmacokinetics (PK) and the pharmacodynamics (PD) of eculizumab were studied in clinical trials for six different indications: paroxysmal nocturnal hemoglobinuria (PNH), idiopathic membranous glomerulopathy (IMG), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis, and psoriasis. Single dose studies of eculizumab were performed in RA and SLE patients, which are reviewed by Dr. Jang-Ik Lee, Clinical Pharmacology Reviewer. Data from multiple dose studies were available from phase-II studies conducted in patients with RA, IMG, and PNH. Also PK/PD data were collected in the

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pivotal trial (C04-001). The present Pharmacometrics review focuses on population PK/PD reports generated from the multiple dose studies and the pivotal trial.

Sponsor's Analysis

Objectives

- To describe the PK of eculizumab and develop a compartmental PK model suitable for population PK analysis of sparsely sampled eculizumab serum concentration data.
- To describe the PK of eculizumab based on data from patients with a variety of diseases.
- To identify clinically important and statistically significant covariates with respect to the PK parameters.
- To explore predicted eculizumab concentration variability in PNH patients using the derived model parameter estimates from PNH patients in a simulation analysis.
- To describe the relationship between eculizumab activity (PD) (as assessed by a serum complement hemolysis assay) and eculizumab concentrations, and to link the PD data to the PK data in a direct PK/PD model.
- To assess PK/PD data collected from PNH patients with the developed models.

Data

Total concentrations (bound + free) of eculizumab in human serum samples (PK) were measured using a validated enzyme-linked immunosorbent assay (ELISA) method. The complement hemolytic activity in serum (PD) were measure using an *ex vivo* hemolytic assay.

These PK/PD data were collected from patients diagnosed with 6 different diseases (RA, IMG, psoriasis, PNH, and SLE). In these studies, 6 dose levels and 6 schedules were used. PK/PD data from a total of 209 patients who participated in 5 clinical trials was used to develop the PK/PD models. These studies included C97-001, C97-002, C01-004, C02-001, and C99-004.

In addition, PK/PD data from patients with a diagnosis of PNH who participated in the pivotal trial (C04-001) was subsequently analyzed with the models after they had been developed.

The PK/PD data in the PNH patients was obtained following multiple doses at trough and 1-hour post-dose. The PK/PD sampling for the 11 PNH patients in the C02-001 study included 4 sets of trough and 1-hour postdose peak samples for each patient. These were obtained at the first dose, at 2 doses in the middle portion of the study, and at the last dosing interval. A mid-interval (1-week postdose) sample was also obtained in mid study. PK and PD samples in the C04-001 (N=40) were drawn at baseline. Continuing into the treatment

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period, trough and peak samples were drawn at Weeks 1, 4, 6, 12, and 26. A trough sample was obtained at end of study. The dosing regimen studied in the PNH studies were same and are described under Introduction.

The summary of the patient demographics for the population PK/PD analysis is shown in Table 1 below.

Table 1: Patient demographics for PK/PD model development (per sponsor PK/PD report)

	Age (y)	Height (cm)	Weight (kg)	SCr (mg/dL)	Dose (mg/kg)
N	209	198	209	209	209
Min	19.0	132.0	48.5	0.5	2.0
Max	84.0	195.0	157.2	2.2	16.8
Median	52.0	168.0	84.0	0.9	8.0
Mean	52.0	169.2	85.4	0.9	7.9
SD	13.56	10.46	20.43	0.27	1.89

Methods

Compartmental models were fitted to the data to obtain the estimates of the population-derived PK parameters using the USC*PACK suite of software. Specifically, the IT2B as well as the NPAG (an improved version of the nonparametric expectation maximization fitter [NPEM]) were used. Other software and programs used to analyze the data were: SAAM II and SAAM II Population Kinetics, GNU G-77 and G-95 Fortran Compiler, ActivePerl 5.8.7, JMP® version 5.01 for Windows®.

All data fitted was weighted by the reciprocal of that datum estimated variance. Weighting was accomplished by making the assumption that total observation variance was proportional to assay variance. A rough estimate of the assay error, as computed by the USC*PACK assay procedure was used throughout this analysis. The analysis could also be performed with adaptive gamma (γ), a scalar that multiplies the polynomial described above and is optimized with each cycle. The objective functions, as well as other measures of goodness-of-fit including mean error, mean squared error, and Akaike information criterion (aic) were used to construct and select the most appropriate model.

Covariate Analyses

Covariates of eculizumab PK parameter estimates were explored using a cluster analysis in all 209 patients. In addition, a 1-way analysis of variance (ANOVA) was performed for each variable: gender, race, age, height, weight, and estimated creatinine clearance (CCr) with each of the PK parameters from the final model for the 209 patients in whom adequate data were suitable for analysis. Each of the PK parameters was subjected to analysis for each of the variables

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and for relationships with each other. The model was fit using JMP 5.01 statistical discovery software from SAS Institute, Inc.

Population Variability – Monte Carlo Simulation

A Monte Carlo simulation of estimated PNH patient PK parameters were derived from the model parameter means and SDs from the 11 PNH patients studied in study C02-001 and fit with the final population PK model. A Monte Carlo simulation was done exploring a maximum variability of 2 SDs of all 5 PK parameters conducted randomly and simultaneously. Three dosing regimens were simulated: 600 mg given weekly 4 times followed by 600 mg Q2wks, 900 mg given weekly 4 times followed by 900 mg Q2wks, and 600 mg given weekly 4 times followed by 900 mg Q2wks beginning 1 week after the last 600-mg dose.

Model Assessment with Data from the Phase 3 PNH Study (C04-001)

The population variability simulation for PNH patients was updated with sparsely sampled PK data from 40 PNH patients who participated in the C04-001 (TRIUMPH) pivotal study. This updated data were analyzed with the models.

PK/PD Relationship

The relationship of the eculizumab concentrations with the PD measurement of hemolysis was explored using maximum PD effect (Emax) model of hemolysis inhibition and eculizumab concentrations. The data set used included paired eculizumab concentration and % hemolysis data from 209 patients: 11 with PNH, 121 with RA, 71 with IMG, and 6 with SLE. The model was fitted using JMP 5.01 software.

The PD effect of eculizumab binding to C5 was evaluated using an assay that measures the % hemolysis of antibody-coated RBCs. Antibody-coated chicken RBCs are very sensitive to lysis by the presence of the membrane attack complex formed by the formation of C5b-9, the terminal product of the complement cascade. These RBCs lyse when small amounts of C5b-9 deposit on the cell membrane and thus are a sensitive measure of complement lysis activity. This complement hemolysis assay served as the primary assay to determine the effectiveness of eculizumab in blocking terminal complement activity in serum of patients. The assay had a steep dose-response curve because of the sensitivity of the antibody-coated RBCs.

Hemolysis data was inverted and normalized by subtracting every datum from the maximum value recorded for that particular patient.

Results

Pharmacokinetic modeling

A total of 39 models were explored to characterize total eculizumab serum concentration – time profile. None of the simple linear models tested could describe the complete data set without significant individual bias. This included

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regular 2- and 3-compartment models, which gave a fairly good overall fit of the data, but showed considerable bias in selected single-dose (data-rich) patients. The PK of total concentrations of eculizumab were, best characterized by a model with 2-compartments with a nonlinear element expressed as the central volume of distribution expanding as a linear function of the mass in the central compartment (LVF model) using the single dose data. Mass exchange was parameterized either by rate constants or by the corresponding clearance (CL) and volume terms (V). The schematic representation of the model is shown in Figure 1 below. The mean parameter predictions are shown in Table 2 below. Bivariate fits of the observed and the predicted by individual parameter estimates and mean estimates are shown in Figure 2. Further results from the application of this model to the 4 patient populations are shown in Table 3. The results of the fitting for the single-dose and the multiple-dose data are shown Figure 3.

Figure 1: Schematic representation of the final pharmacokinetic model (2-compartment with mass-dependent linear volume expansion)

Differential equations:

$$\frac{dX_{(1)}}{dt} = R_{in} - \left[\frac{CLd2}{V1 + (A + X_{(1)})} \right] \cdot X_{(1)} + \left[\frac{CLd2}{V2} \right] \cdot X_{(2)}$$

$$\frac{dX_{(2)}}{dt} = \left[\frac{CLd2}{V1 + (A + X_{(1)})} \right] \cdot X_{(1)} - \left[\frac{CLd2}{V2} \right] \cdot X_{(2)}$$

Output:

$$Y = \left[\frac{X_{(1)}}{V1 + (A + X_{(1)})} \right]$$

Legends:

- n: Compartment number
- X_0 Dose
- $X_{(n)}$ Mass in Compartment n (at time t)
- V_n Volume associated with Compartment n
- CL Clearance (elimination)
- CLd2 Inter compartmental clearance

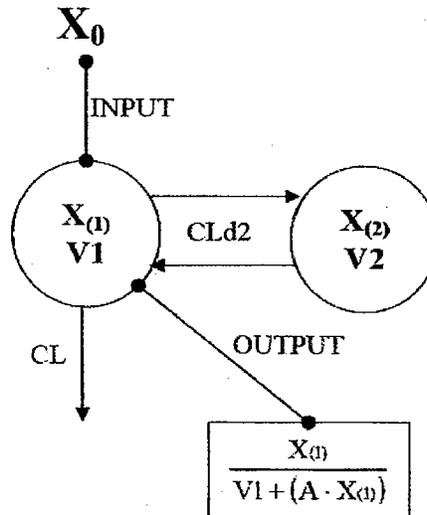


Table 2: Mean parameter predictions for the final pharmacokinetic model (Mass-dependent linear volume expansion) from single dose patients only

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Model and Statistic	AUC _{tr} (hr*µg/mL)	CL (area) (mL/hr)	CL (mL/hr/kg)	CL ₂ (mL/hr/kg)	V ₂ (mL/kg)	A (mL/µg)	V ₁ (mL/kg)
2CLVFCL							
Mean	26161	0.2589	0.3391	0.8256	25.777	0.003821	19.0635
SD	12772	0.0837	0.2724	1.3097	24.751	0.001059	12.1166
Median	28756	0.2315	0.2350	0.4756	25.019	0.004175	17.8632
% SD	48.8	32.3	80.3	158.6	96.0	27.7	63.6

Figure 2: Bivariate fit of (a) Observed by Individual predicted and (b) Observed by Mean predicted

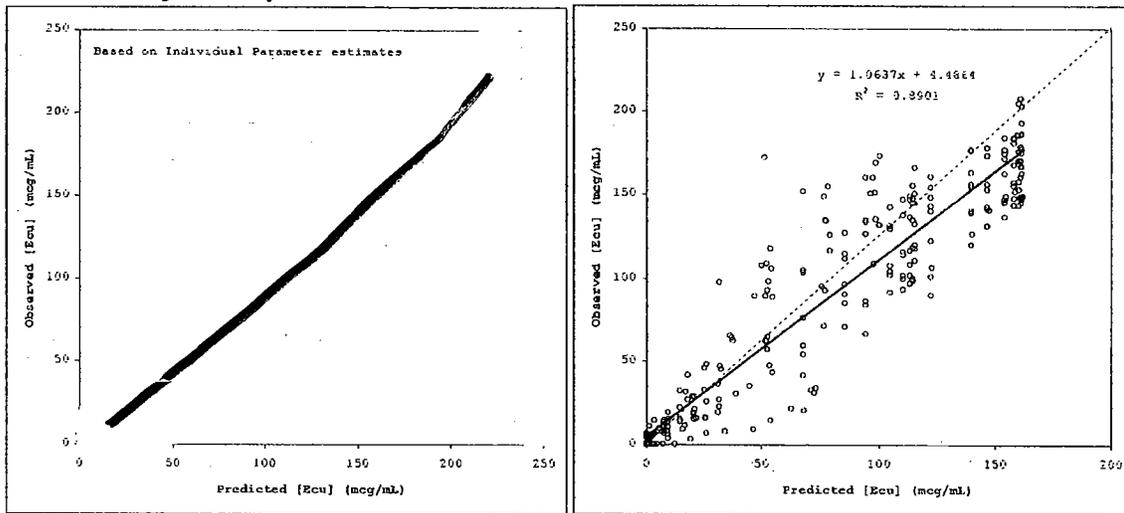
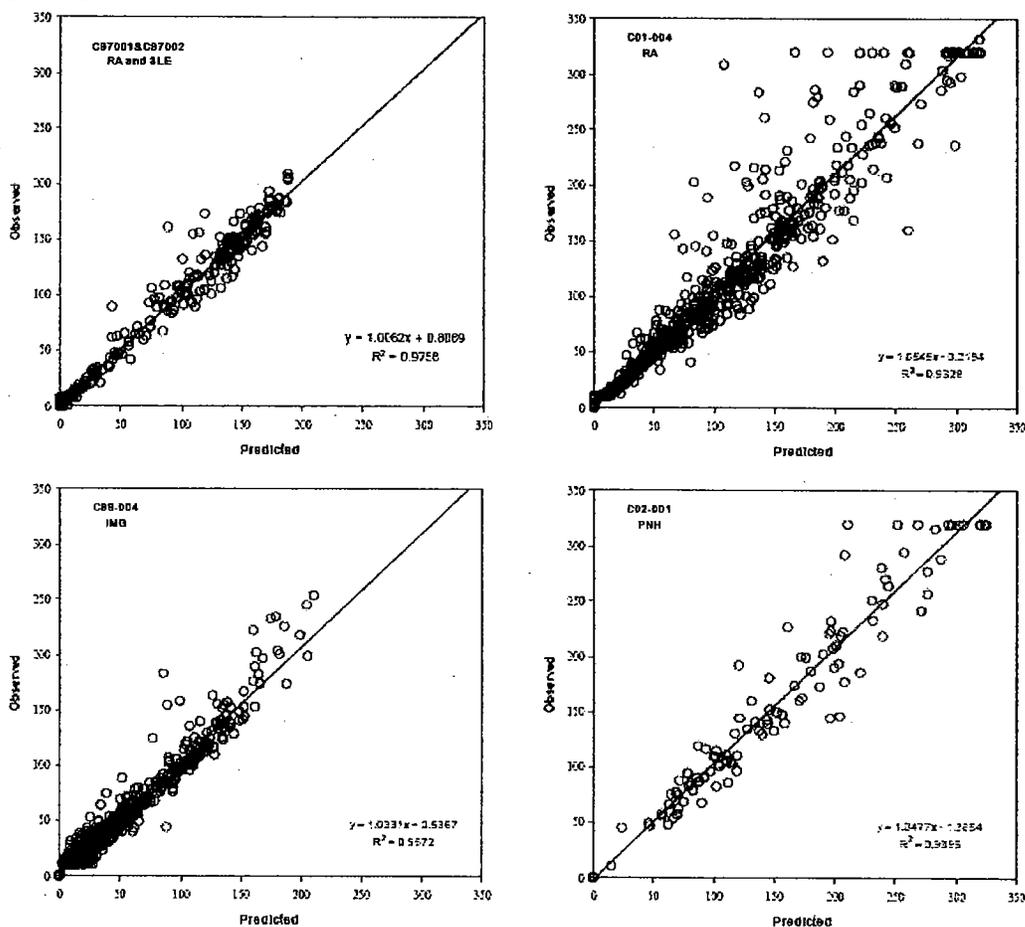


Table 3: Mean parameter predictions for the final pharmacokinetic model (Mass-dependent linear volume expansion) from the entire database

	IMG N=71		PNH N=11		RA N=121		SLE N=6		Total N=209	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CL (mL/hr/kg)	0.41	0.139	0.25	0.069	0.30	0.117	0.30	0.106	0.333	0.134
CL ₂ (mL/hr/kg)	0.21	0.174	0.21	0.055	0.54	0.156	0.59	0.562	0.43	0.241
V ₂ (mL/kg)	149.5	44.92	26.5	7.37	42.3	9.68	20.6	10.84	77.5	58.70
A (mL/µg)	0.000	0.000	0.002	0.001	0.004	0.000	0.004	0.0004	0.002	0.001
	7	21	0	42	2	75	0	2	9	8
V ₁ (mL/kg)	64.9	31.53	32.5	16.50	12.7	8.54	18.7	4.84	31.66	31.32

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Figure 3: Bivariate fit of observed and predicted eculizumab concentrations for the single-dose and multiple-dose studies for the different diseases

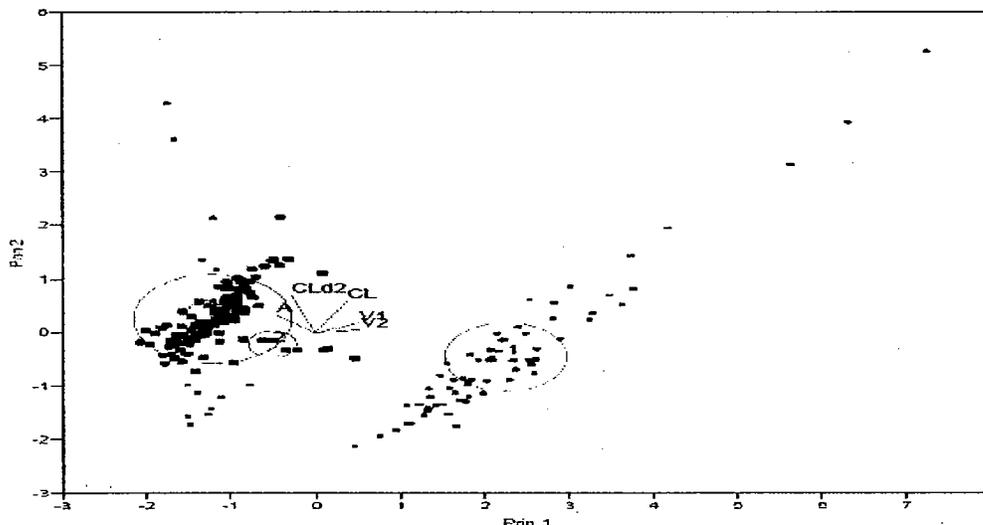


Analysis of Covariates

Patients with a diagnosis of IMG were found to be different from patients with the other diseases studied with regard to the PK parameter estimates when analyzed in a cluster analysis. The cluster analysis included all parameters estimated (CL, CLd2, V2, A, V1) with the number of allowed clusters set to the number of tested indications (IMG, RA, PNH, and SLE). The IMG patient group had higher total CL and Vd than did the other patient groups as shown in Figure 4 and Table 4. Statistically significant correlations were observed for a number of the covariate/parameter pairs, including body weight vs CL in both IMG and the other disease indications. While these covariate/parameter pairs appear to be statistically correlated, there were PD observations which demonstrated these correlations were not clinically relevant. Consequently no covariates, apart from IMG were incorporated in the final compartmental model.

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Figure 4: Bi-plot of K-means Cluster Analysis of Parameter Distributions: Cluster Centers Linked to Indication



Cluster 1- IMG; Cluster 2- PNH; Cluster 3- RA; Cluster 4- SLE

Table 4: Cluster summary statistics for different disease states

Indication	CL (mL/hr/kg)	CL _{d2} (mL/hr/kg)	V ₂ (mL/kg)	A (mL/μg)	V ₁ (mL/kg)
IMG	0.41±0.139	0.21±0.174	149.57±44.924	0.000699±0.000207	64.908±31.529
PNH	0.26±0.066	0.543±0.168	29.97±8.094	0.0019±0.00148	32.51±16.289
RA	0.29±0.117	0.542±0.155	42.30±9.680	0.0042±0.00074	12.72±8.541
SLE	0.304±0.106	0.591±0.562	20.57±10.835	0.00397±0.00042	18.74±4.843

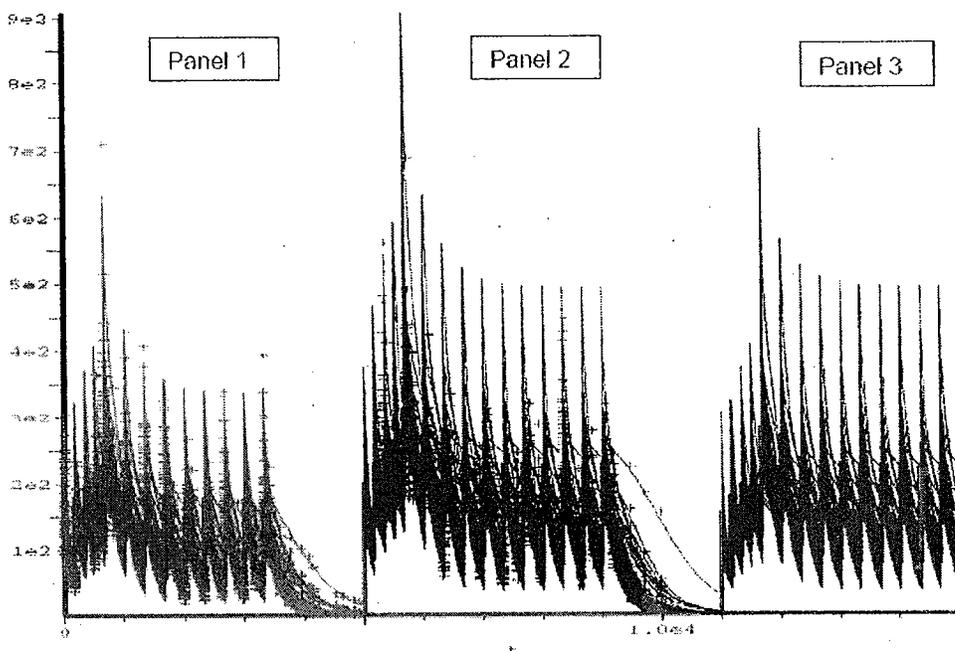
Data expressed as mean ± SD

Population Variability – Monte Carlo simulation

A Monte Carlo simulation was conducted exploring a maximum variability of 2 SDs of all 5 PK parameters conducted randomly and simultaneously. The simulated PK parameters were derived from the model parameter means and SDs from the 11 PNH patients studied in study C02-001 and fit with the final pharmacokinetic model (2-compartment with mass-dependent linear volume expansion). Three dosing regimens were simulated: 600 mg given weekly for 4 weeks followed by 600 mg Q2wks (Figure 5: 1st panel); 900 mg given weekly for 4 weeks followed by 900 mg Q2wks (Figure 5: 2nd panel), and 600 mg given weekly for 4 weeks followed by 900 mg Q2wks beginning 1 week after the last 600 mg dose (Figure 5: 3rd panel; dose schedule used to treat PNH patients). The serum concentrations in the simulations show acceptable variability, as they are relatively well conserved in the population. Also the simulations indicate that excessive accumulation does not occur in PNH patients.

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Figure 5: Monte carlo simulation of eculizumab concentrations in 50 simulated PNH patients based on PNH patient mean parameters from the final pharmacokinetic model



Concentrations in $\mu\text{g/mL}$ are plotted on the y-axis in scientific notation as 10 raised to the exponent. The time frame is plotted on the x-axis in hours raised to the exponent.

Analysis of PK in the Pivotal Trial

A standard 1-compartmental model analysis on the C04-001 patients' sparsely sampled PK data was conducted. The summary of the parameter mean estimates from the compartmental analysis are shown in Table 5 below.

Table 5: Parameter mean estimates of the data in PNH patients from pivotal trial (N=40, 1-compartment model)

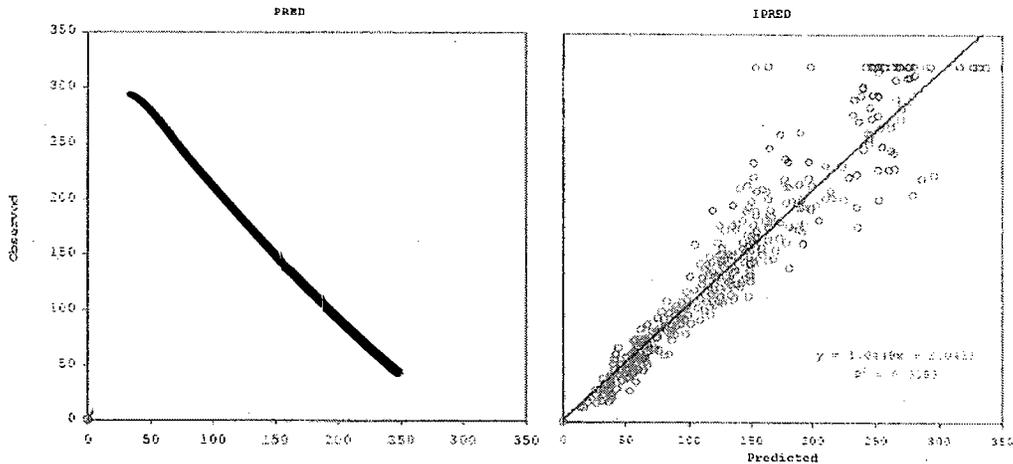
	CL (mL/hr/kg)	V_d (mL/kg)	K_{el} (1/hr)	$t_{1/2}$ (hr)
Mean	0.311183	110.3	0.002776	271.7
SD	0.125097	17.9	0.000817	81.6
% SD	40.20	16.2	29.45	30.0
Min				
Max				
Median	0.289969	108.3	0.002793	248.2

1C-p = 1CPNCLI; 1-compartment clearance parameterization IT2B method

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A 1-compartment model with mass-dependent volume expansion model did not result in improved fit of the data; hence the parsimonious model was preferred. Bivariate fits of the observed and the predicted by individual parameter estimates and mean estimates are shown in Figure 6.

Figure 6: Bivariate fit of (a) Observed by Individual predicted and Mean predicted

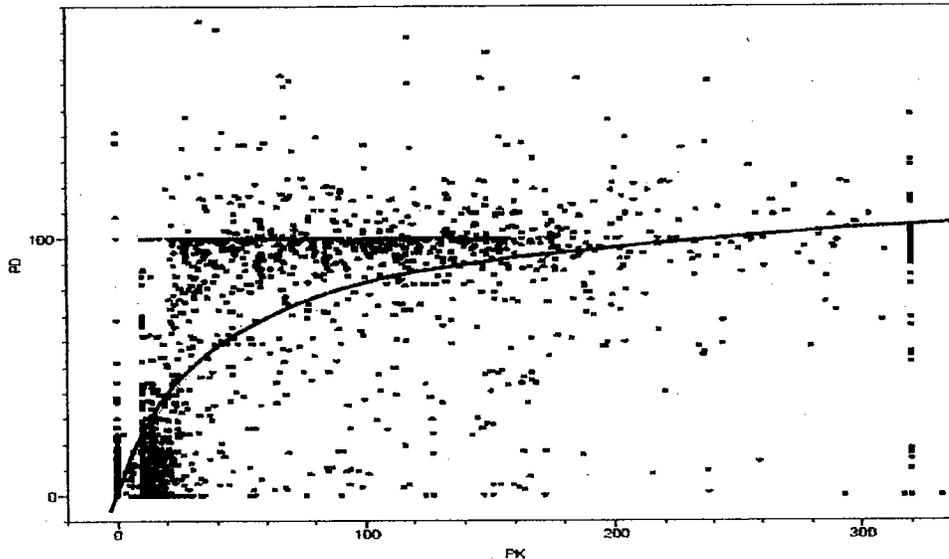


PK/PD Relationship

The relationship between eculizumab concentrations and C5 activity as measured by a serum complement hemolysis assay was described using a simple Emax model. The fit of the data to the Emax model was acceptable (Figure 7) given the limits of the assay, number of points, and patients involved. The x-axis in Figure 7 represents eculizumab concentrations and the y-axis the inverted normalized % hemolysis in the paired samples. The samples were obtained at anytime after dosing had begun during the relevant study. The 2 offsets seen on the y-axis are caused by the BLQ samples being set to zero or to ∞ . The Emax was estimated to be $118\% \pm 27\%$ hemolysis (95% CI for the mean is 114-123%). The E50 was estimated to be $43 \pm 2.7 \mu\text{g/mL}$ (95% CI for the mean is 39-48 $\mu\text{g/mL}$). Because the PK assay used to determine eculizumab concentrations in human serum measures both bound and free eculizumab levels, an overestimated EC_{50} of 43 $\mu\text{g/mL}$ reflects the total serum level of eculizumab required to block terminal complement activation.

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Figure 7: Emax model of inhibition of % hemolysis by eculizumab concentrations from patients with IMG, RA and PNH



The x-axis represents eculizumab concentrations. The y-axis represents the inverted normalized % hemolysis in the paired samples.

Conclusions

- A 2-compartmental LVF PK model suitable for population PK analysis of sparsely sampled eculizumab serum concentration data was developed and validated.
- The PK of eculizumab was adequately described by the selected model based on data from patients with a variety of diseases.
- No clinically important covariates with respect to the PK parameters were found.
- Population eculizumab concentration variability in PNH patients was explored using the derived model parameter estimates from PNH patients in a Monte Carlo simulation. In this analysis, no excessive accumulation of eculizumab was observed.
- The relationship between eculizumab concentration and hemolytic activity was described using a simple Emax PK/PD model.
- PK/PD data collected from PNH patients were assessed with the developed models and were found to fit well to accurately predict PK parameters.
- A successful link between the mass-dependent linear volume expansion model and PD response (hemolytic activity) was described.

Reviewer's Comments

The conduct of the population pharmacokinetic analysis, PK/PD analysis and the interpretation of the results were reasonable.

The following are the comments:

- It is unclear as to the purpose of two different population analyses – (i) analysis conducted from the data derived from SLE, RA, IMG and phase II PNH data - a two compartment model with mass-dependent linear volume expansion model and (ii) one compartment analysis of the data derived from the phase III pivotal trial in PNH patients.
- One of the objectives of the report was to assess the models developed from the data in different disease states with the data from PNH patients from the phase III C04-001 study. Instead of testing the two compartment model developed, the sponsor chose to develop a different model.

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Reviewer's Analysis

Objective

The focus of the analysis was aimed at characterizing the time course of the lactate dehydrogenase (LDH) levels, a description of the pharmacodynamics of eculizumab, in the pivotal trial (C04-001).

Introduction

LDH has long been considered as a useful marker of intravascular hemolysis¹. Its serum levels are mildly elevated in extravascular hemolysis, such as immune hemolytic anemia, but are substantially elevated with intravascular hemolysis, such as thrombotic thrombocytopenic purpura and PNH². RBCs contain large amounts of LDH, and quantitation of total LDH and hemoglobin in osmotically lysed RBCs show a near uniform correlation between these parameters *in vitro*³.

Data

LDH levels as a part of the clinical chemistry monitoring in the pivotal trial (C04-001) were collected in the trial at Visits 1, 2, 3 (Baseline), 4, 5, 6, 7, 9, 11, 13, 15, 17 and 18 or early termination. From baseline the visits corresponded to Study weeks of 0, 1, 2, 3, 4, 8, 12, 16, 20, 24 and 26, respectively.

Method

Descriptive statistics for LDH levels on placebo and eculizumab treatment were derived at each of the visits and the time course of LDH were plotted. Exposure-LDH relationship could not be modeled using the routine PK/PD modeling as the time course of LDH following single dose was not available. Further, the available trough and peak eculizumab concentrations available from the trial corresponded to a significant effect, making it difficult to get a precise estimate of the EC₅₀.

Results

A summary of the levels of LDH over the time course of the trial for placebo and eculizumab treatment arms is shown in Table 6. A graphical representation of the same data is shown in Figure 8. It is clearly evident that LDH levels are decreased at least 3 fold by end of the first dose (week 1) and this effect is consistently maintained over the duration of the treatment. LDH levels at baseline are approximately 10 times the upper limit normal (ULN) and by the

¹ Kato et al. *Blood*, 15 March 2006, Vol 107, No. 6; 2279-2285.

² Tabbara IA. *Med Clin North Am.* 1992; 76: 649-668.

³ Van Lente et al. *Clin Chem.* 1981; 27:1453-1455.

Eculizumab (Soliris®)

second week the levels on eculizumab treatment are reduced to approximately 1.5 X ULN. However, the LDH levels on placebo are unchanged from baseline to week 26. The huge standard deviation at the latter visits on treatment arm was predominantly driven by a single subject (011-001), who had a baseline value of 5962 U/L and 1776 U/L by week 1 and 2984 U/L at week 26.

Table 6: Summary of the LDH levels on placebo during the pivotal trial (C04-001)

N	Visit	Week	Mean	SD
43	3	0	2259.0	1039.2
44	4	1	2215.1	905.1
44	5	2	2250.7	1007.4
43	6	3	2336.4	1049.0
42	7	4	2353.7	940.6
39	9	8	2336.4	996.6
37	11	12	2323.7	1015.9
34	13	16	2356.9	781.3
33	15	20	2318.0	752.6
33	17	24	2199.7	790.6
34	18	26	2294.4	864.5

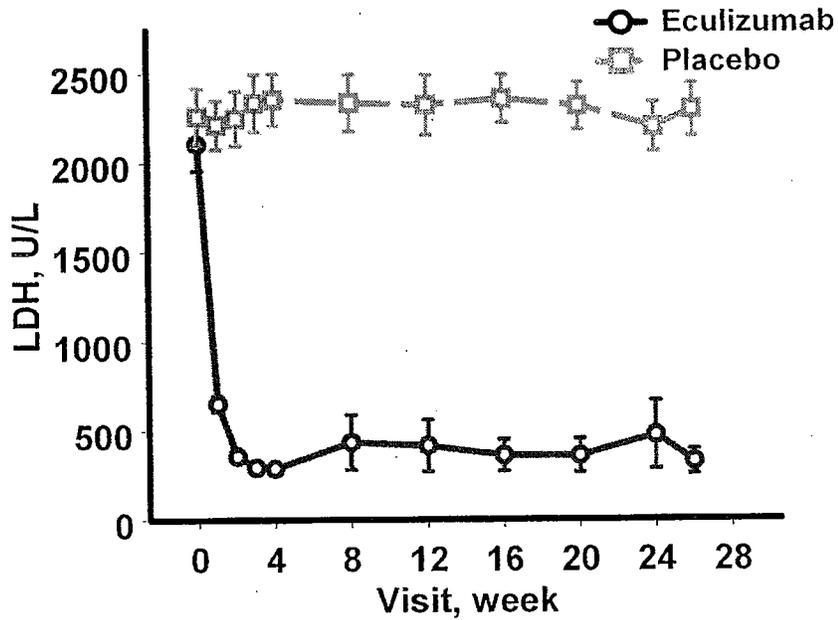
Table 7: Summary of the LDH levels on eculizumab during the pivotal trial (C04-001)

N	Visit	Week	Mean	SD
41	3	0	2108.5	965.3
41	4	1	651.9	278.3
40	5	2	359.3	100.7
41	6	3	294.7	97.3
41	7	4	289.6	168.6
40	9	8	436.0	975.6
40	11	12	415.8	925.1
40	13	16	361.5	556.7
39	15	20	358.8	596.9

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N	Visit	Week	Mean	SD
39	17	24	475.8	1194.2
40	18	26	325.9	438.3

Figure 8: Treatment with Eculizumab results in immediate and sustained lowering of LDH levels



Conclusion

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