22 September 2011
EXT/834951/2011 Corr[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Soliris

eculizumab

Procedure No.: EMEA/H/C/000791/II/0027

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] Deletion of commercially confidential information

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22 September 2011
EMA/785583/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP variation assessment report

Type II variation EMEA/H/C/000791/II/0027

Invented name/name:	Soliris
International non-proprietary name/common name:	eculizumab
Indication summary (as last approved):	treatment of paroxysmal nocturnal haemoglobinuria (PNH)
Marketing authorisation holder:	Alexion Europe SAS

1. Scope of the variation and changes to the dossier

Scope of the variation:	Extension of indication of Soliris in the treatment of atypical haemolytic uremic syndrome (aHUS). Consequently sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Summary of Product Characteristics (SmPC) have been updated. In addition additional vaccination and antibiotic prophylaxis recommendation are reflected in sections 4.4 and 6.6 of the SmPC. The PL has been updated accordingly. Furthermore the MAH took the opportunity to update the product information with the latest version of the QRD template.
Rapporteur: Co-Rapporteur:	Arantxa Sancho-Lopez Pierre Demolis
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	1,2 and 5

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Product Information affected:	SmPC, Annex II and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	17 March 2011
Start of procedure:	27 March 2011
Rapporteur's and Co-Rapporteur's joint preliminary assessment report circulated on:	30 May 2011
Rapporteur's and Co-Rapporteur's joint updated assessment report circulated on:	22 June 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 June 2011
MAH's responses submitted to the CHMP on:	21 July 2011
Rapporteur's and Co-Rapporteur's joint preliminary assessment report on the MAH's responses circulated on:	08 September 2011
CHMP opinion:	22 September 2011

3. Scientific discussion

3.1. Introduction

Eculizumab is being evaluated for the treatment of patients with atypical haemolytic uraemic syndrome (aHUS) based on the documented role of uncontrolled complement activation in these patients and the mechanism of action of eculizumab to effectively block activation of terminal complement.

Eculizumab is currently approved in the treatment of paroxysmal nocturnal haemoglobinuria (PNH) which has many similarities with aHUS. Both aHUS and PNH are complement inhibitor deficiency disorders characterised by uncontrolled complement activation. aHUS is a very rare, serious and life-threatening disorder characterised by the diagnostic triad of thrombotic thrombocytopenia, microangiopathic haemolysis and impaired renal function as well as other ischemic complications. Most cases of aHUS are secondary to mutations in genes which encode components of the alternative pathway of the complement cascade. Similar to observations in PNH, uncontrolled complement activation may contribute to the thrombotic microangiopathy (TMA) process in aHUS by causing inflammation and prothrombotic activity. Patients with aHUS currently face a very poor prognosis with high likelihood of kidney failure, dialysis and/or death within one year from the time of diagnosis.

While aHUS is a very rare disorder, the incidence of aHUS has been poorly characterised. From the sparse epidemiologic data in the literature, reports indicate that most patients develop the disease before 10 years of age. Data derived from the European HUS registry indicate that only 167 patients have been identified across Europe, and prevalence was estimated at approximately three per million in children less than 18 years of age. The prevalence in adults is expected to be lower.

Patients with aHUS have uncontrolled complement activation, and in approximately half of aHUS cases mutations have been identified in the alternative pathway of the complement cascade, including mutations in genes encoding complement regulatory proteins and/or patients with the presence of neutralising antibodies to these proteins. Mutations have been identified in at least 10 different genes to date. Because of the heterogeneity of different complement defects contributing to clinically severe aHUS, and because only approximately 50% of aHUS patients have observed mutations, identification of a specific mutation is not required for aHUS diagnosis. While many patients with aHUS report a prodrome of feeling unwell, including fever, malaise, diarrhoea, abdominal pain, nausea, vomiting, or neurologic symptoms, patients with aHUS are generally only clinically identified when they present with an abrupt onset of signs and symptoms. If they survive this initial disease presentation, they are typically burdened with a chronic thrombotic and inflammatory state characterised by platelet and endothelial cell activation which carries a life-long elevated risk of sudden blood clotting, renal insufficiency with ensuing dialysis, and other severe complications of TMA. Severe TMA complications in patients with aHUS, in addition to renal TMA complications, include seizures, CNS infarcts, coma, cardiomyopathy, myocardial infarction, pancreatitis, pulmonary distress, diffuse vasculopathy, and multi-organ TMA. These complications frequently lead to premature mortality in aHUS.

Presently there are very limited treatment options for patients with aHUS. Therapy is empirical and aimed primarily at stabilising the patient and mitigating irreversible kidney damage through the use mostly of plasma therapy (PT) and can include the use of immunosuppressant drugs and supportive care. The rationale for the use of PT in aHUS patients is to remove plasma, which contains mutated complement regulatory proteins or auto-antibodies to complement regulatory proteins, and replace it with fresh frozen plasma (FFP) from healthy donors in an attempt to transiently restore control of complement activity. However, there are limited data which support the long-term benefit of PT and no controlled clinical trials have been performed to establish its safety or efficacy in patients with aHUS. In addition, PT is a laborious procedure leading to a poor quality of life for patients who receive it. It is also associated with a risk of infection, allergic reactions, thrombosis, and loss of vascular access and provides incomplete reversal of TMA. Kidney transplant has been undertaken in aHUS patients, however, despite the best supportive care, recurrent aHUS causes kidney transplant failure in up to approximately 60 to 90 percent of patients.

Eculizumab is a high affinity humanised monoclonal antibody (mAb) that binds uniquely to human complement component C5. Eculizumab blocks the cleavage of C5 into the proinflammatory, pro-thrombotic and lytic C5a and C5b-9 complement components, while leaving the upstream components of complement, most notably C3b, intact to preserve opsonisation of pathogens and clearance of immune complexes.

Eculizumab has been approved as the first safe and effective treatment for patients with Paroxysmal Nocturnal Hemoglobinuria (PNH).

This medicinal product was designated in atypical haemolytic uremic syndrome as an orphan medicinal product EU/3/09/653 on 24 July 2009.

The purpose of this type II variation application (C.I.6.a) is to seek approval for Soliris (eculizumab) in the treatment of atypical haemolytic uraemic syndrome.

The MAH proposed the update of sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Summary of Product Characteristics (SmPC). In addition the MAH took the opportunity of this variation to reflect additional vaccination and antibiotic prophylaxis recommendation in sections 4.4 and 6.6 of the SmPC and to update the product information with the latest version of the QRD template. The PL has been updated accordingly.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (P/224/2010) for the following condition(s):

- Treatment of paroxysmal nocturnal haemoglobinuria
- Treatment of atypical haemolytic uraemic syndrome

On the agreement of a paediatric investigation plan (PIP)

The PIP is not yet completed

3.2. Non-clinical aspects

Ecotoxicity / environmental risk assessment

According to the CHMP guideline "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (ref. EMEA/CHMP/SWP/4447/00, dated 01 June 2006), 'Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment. Similarly, vaccines and herbal medicinal products are also exempted due to the nature of their constituents'.

Eculizumab is a natural substance (protein), the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, eculizumab is not expected to pose a risk to the environment.

3.3. Clinical aspects

3.3.1. Introduction

Alexion has conducted two prospective open-label single-arm clinical trials (Study C08-002A/B and Study C08-003A/B) in adult and adolescent patients with aHUS and a retrospective data collection study (Study C09-001r) to capture the information on adult and paediatric patients who received eculizumab outside of the prospective clinical trials, to support the registration of eculizumab in the treatment of aHUS.

Table 1: Studies Supporting the Safety and Efficacy of Eculizumab in aHUS

		Number of patients		
Study	**Population**	**Accrual Target**	**Enrollment**	**Treated**
C08-002A/B	PT-resistant	Up to 15	17	17
C08-003A/B	PT sensitive (chronic PT)	Up to 30	23	20
Total prospective controlled studies			40	37
C09-001r	aHUS	36*	30	30
Total Application			70	67

*Target based on the number of patients Alexion was aware of through Physician communication

CHMP guidelines / Scientific Advice

The MAH did not seek CHMP scientific advice for this application.

GCP aspects

According to the MAH, the clinical trials included in this application were conducted in accordance with the principles of Good Clinical Practice, as defined by the International Conference on Harmonization. All studies were performed to meet the ethical requirement of Directive 2001/20/EC and FDA GCP regulations.

3.3.2. Clinical Pharmacology

The formulation, presentation and administration of eculizumab in studies C08-002A/B and C08-003A/B were identical to those described in the SmPC. These have been previously described in the original PNH submission.

Data from PNH clinical studies in adults have shown that eculizumab serum concentrations greater than 35 µg/mL blocked serum terminal complement activation and resulted in a rapid reduction in intravascular hemolysis in the majority of patients. The targeted eculizumab concentration of 35 µg/mL is consistent with its stoichiometric binding to C5, since eculizumab and human C5 are similar in molecular weight, eculizumab binds two molecules of C5 and endogenous concentrations of C5 had been previously reported to range from approximately 70 to 90 µg/mL.

However, elevated LDH levels, indicating breakthrough hemolysis and incomplete terminal complement inhibition, were occasionally observed in patients with PNH being treated with the PNH specific dose regimen.

Due to the potential rapid loss of kidney function that can occur in patients with aHUS experiencing TMA, breakthrough from terminal complement inhibition was considered clinically unacceptable. In fact, it was considered critically important to optimise the induction and maintenance dose of eculizumab for the treatment of aHUS patients to maintain complete and sustained terminal complement inhibition and to address the higher free C5 levels observed in patients. Therefore, a target trough level was chosen (e.g., 50-100 µg/mL), which also accounts for sufficient eculizumab levels in patients with higher endogenous C5 levels or for patients with a higher drug clearance rate.

In order to develop an optimal dosing strategy for aHUS, meta-analysis was performed using data from all PNH studies (C02-001, C04-001, C04-002, E05-001 and C07-001) to assess the PK of eculizumab in PNH patients, establish the relationship between plasma concentrations of eculizumab and the percent of haemolytic activity and ultimately identify sources of variability in PK/PD parameters of eculizumab. Of the 224 PNH patients exposed to eculizumab during clinical development, a total of 177 patients provided samples for PK and PD analyses. A total of 85 male and 92 female patients were included in the analysis. A one-compartment PK model parameterized with clearance (CL) and volume of distribution (Vc) fitted the plasma concentration profiles of eculizumab adequately. Results from the current population PK analysis suggest that the proposed dosing strategy in PNH resulted in a close-to-full inhibition of haemolytic activity in PNH patients. Furthermore, eculizumab treatments were well tolerated during the induction and maintenance treatment phases. The above population PK model was used to support the proposed eculizumab dosing strategy for aHUS patients with a targeted trough level of 50-100 µg/mL.

Dosing simulations were conducted for adults, adolescents and paediatric patients leading to a weight based dosing recommendation for aHUS patients.

Pharmacokinetic and pharmacodynamic data were collected from the 37 patients included in the two prospective controlled studies (C08-002A/B and C08-003A/B). In addition, selected pharmacokinetic and pharmacodynamic data were performed on a voluntary basis without a specific schedule of collection from 20 patients who participated in the retrospective study (C09-001r).

3.3.2.1. Pharmacokinetic data

A pharmacokinetic simulation was conducted to model the target eculizumab dose in aHUS patients in order to maintain a trough level 50-100 µg/ml.

The target C_{min} eculizumab serum concentration was set at 50-100 µg/mL to provide adequate drug exposure for complete and sustained inhibition of terminal complement activity throughout the 26 week dosing treatment period. The target Cmax was set at <700 µg/mL which was the highest concentration observed during the conduct of the PNH clinical trials and proved to be a safe level of exposure to eculizumab. A trial simulation model was used to define the optimal dosing regimen in adult patients. This model was repeated for various weight groups. Based on the results of these simulations, the following weight-based doses and dose schedules were recommended for aHUS patients:

Table 2: Dosing Recommendations in aHUS Patients

Group	Induction Dose	Maintenance Dose
≥ 40 kg*	900 mg Weekly for 4 Weeks	1200 mg at Week 5 then Every 2 Weeks
30 – <40 kg	600 mg Weekly for 2 Weeks	900 mg at Week 3 then Every 2 Weeks
20 – <30 kg	600 mg Weekly for 2 Weeks	600 mg at Week 3 then Every 2 Weeks
10 – <20 kg	600 mg Weekly for 1 Week	300 mg at Week 2 then Every 2 Weeks
5 – <10 kg	300 mg Weekly for 1 Week	300 mg at Week 2 then Every 3 Weeks
*Dosing recommendation applicable for all adult and adolescent aHUS patients		

A similar PK simulation was performed to assess the effect of plasma therapy on eculizumab concentration. In the population PK model, PT interventions resulted in a marked increase in systemic clearance of eculizumab and a marked reduction in the elimination half-life. Based on the PK modelling, it was estimated that a supplemental eculizumab dose of 600 mg was required within 60 minutes prior to each 2 units of fresh frozen plasma or within 60 minutes after each plasmapheresis or plasma exchange.

The analysis of C_{min} and C_{max} from the two prospective controlled studies and the retrospective data collection validated the dosing scheduled derived from the PK modeling in aHUS patients at all ages (Table 3). During the induction dosing phase, the mean C_{min} concentration ranged from 90 µg/mL to 171 µg/mL. During the maintenance dosing phase, the eculizumab mean C_{min} concentration range was maintained between 94 and 234 µg/mL. During both the induction and the maintenance phase mean C_{max} remained under the set target value of < 700 µg/ml.

Within the adult and adolescent groups, PK parameters were consistent across all three studies. PK parameters were also consistent across all age groups although C_{min} tended to be higher in the paediatric patients during the induction phase than in adult and adolescent aHUS patients.

Table 3: PK Parameters in Studies C08-002A/B, C08-003A/B and C09-001r

		Induction			Maintenance		
		AUC (µg.h/mL)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg.h/mL)	C_{max} (µg/mL)	C_{min} (µg/mL)
Adults (>18 Years)							
Study C08-002A/B	N=16	19,611	145	93	77,693	342	149
Study C08-003A/B	N=15	22,928	163	113	104,228	431	214
Study C09-001r	N=4	20,537	161	90	63,028	316	100
Adolescent (12-18 years)							
Study C08-002A/B	N=1	20,905	147	104	95,117	392	196
Study C08-003A/B	N=5	22,084	157	109	99,956	414	205
Study C09-001r	N=2	28,908	222	130	95,242	457	161
Pediatric*							
6 -<12 years	N=5	31,299	223	154	113,954	473	234
2-<6	N=4	39,537	316	171	56,583	278	94
<2years	N=5	36,406	281	166	95,990	367	121
All data summarized as mean value * All patients from study C09-001r							

Source: Module 2.7.2

3.3.2.2. Analytical methods

Analytical tests used during the clinical development of eculizumab in human clinical trials for patients with aHUS and the methods used are summarised in Table 4.

Table 4: Summary of analytical tests

Analytical Tests Used in the Clinical Development of Eculizumab	Methods Unchanged Since Application for PNH [1]	Methods Modified Since Application for PNH	New Analytical Tests	Commercial Analytical Test	Analytical Test Methods Described in this Module
Pharmacokinetic assay (Eculizumab concentration in human serum)	BTM-0013	SOP-G-BTM-0056	NA	NA	1.2.1
Pharmacodynamic assay (C5 activity in human serum as measured by hemolysis)	BTM-0010[2]	NA	NA	NA	1.2.2
Soluble terminal complement complex assay (quantitative assay to measure C5b-9 concentration in human plasma)	NA	NA	NA	SOP-LUS-BTM-0052[3]	NA
C5 level (concentration of human C5 in human serum)	NA	NA	BTM-0053	NA	1.2.3
HAHA (immunogenicity assays to detect human anti-human antibodies and neutralization potential)	NA	NA	BTM-0047 BTM-0048	NA	1.2.4

[1] PNH = paroxysmal nocturnal hemoglobinuria
[2] Cross reference the original module 5.3.4.2
[3] The commercial test platform used is BD Opt EIA Human C5b-9 ELISA Set (BD Biosciences, Cat. No. 558315)
NA = Not Applicable

3.3.2.3. Two Pharmacokinetic (PK) assay methods were used to measure total serum eculizumab: the original method described in BTM-0013 and an updated method described in SOP-G-BTM-0056. The assay range of 10 - 320µg/mL associated with BTM-0013 led to a relatively high number of Above Limit of Quantitation (ALQ) concentration values in post-dose samples of patients from the aHUS clinical trials, possibly reflecting the higher doses of eculizumab that these patients received in comparison to patients with PNH. To address this, the assay dynamic range was widened in SOP-G-BTM-0056. These changes allow a significantly expanded assay range with the reliability to measure eculizumab sample concentrations ranging from 9.4 to 600µg/mL. This range spans most of the peak concentration values of eculizumab in patient samples. SOP-G-BTM-0056 was validated and reported in BTMV-0020FR , and was used to measure eculizumab concentrations for several of the patients from the C09-001r trial.Population PK modelling using pooled data from prospective and retrospective studies

A population PK analysis was performed using all the available data from the prospective and retrospective studies. The model parameters for the pooled data were estimated using a structural model.

In order to evaluate the effect of the retrospective study data on population PK parameters of eculizumab collected in prospective trials, a “study effect” on CL and Vc of eculizumab was tested and was found to be not significant at the 5% level (P-value>0.05). These results suggest that the PK parameters of eculizumab in aHUS patients from the prospective and retrospective studies were similar.

Table 5: Eculizumab – Population PK Parameters – Pooled Data

Population PK Parameters[a]	Prospective[b] Studies	Prospective and Retrospective Studies[c]
Systemic Parameters		
CL (L/h)[d]	$CL = 0.0139 \times \left(\frac{\text{Body Weight}}{70}\right)^{0.764}$	$CL = 0.0146 \times \left(\frac{\text{Body Weight}}{70}\right)^{0.669}$
V_c (L)	$Vc = 5.95 \times \left(\frac{\text{Body Weight}}{70}\right)^{0.143}$	$Vc = 6.14 \times \left(\frac{\text{Body Weight}}{70}\right)^{0.722}$
Correlation between CL and Vc	45.8%	No correlation
Between Subject Variability		
On CL	29.6%	33.9%
On V_c	25.3%	20.9%
Error Model		
Additive error (µg/mL)	0 Fix	23.0
Proportional error (%)	30.7	31.9

[a] CL=Clearance of eculizumab, PE= Plasma exchange, V_c= Volume of central distribution of eculizumab.
[b] Protocols C08-002A/B and C08-003A/B
[c] Protocols C08-002A/B, C08-003A/B and C09-001r
[d] When aHUS patients undergo plasma exchange, CL of eculizumab in the prospective study was 3.35 L/h during the PE intervention. When combining the prospective and retrospective studies, CL of eculizumab was 3.66 L/h during the PE intervention

3.3.2.4. Pharmacodynamics

Eculizumab is a high affinity humanised monoclonal antibody (mAb) that binds uniquely to human complement component C5. Eculizumab blocks the cleavage of C5 into the proinflammatory, pro-thrombotic and lytic C5a and C5b-9 complement components, while leaving the upstream components of complement, most notably C3b, intact to preserve opsonization of pathogens and clearance of immune complexes.

No additional clinical pharmacodynamic studies were submitted in this application.

3.3.2.5. Discussion on clinical pharmacology

The threshold of 35 µg/ml as the minimum level that blocked serum terminal complement activation is considered acceptable, however a complete complement inhibition cannot be ensured. The MAH´s proposal to increase the trough concentration of eculizumab (50-100 µg/ml) in aHUS in order to get a better efficiency of the pharmacodynamic appears well motivated to the CHMP.

According to the data from the prospective studies, overall, the objective of 50-100 µg/ml has been achieved in the induction and maintenance phase. The mean C_{min} was shown to be clearly superior. Interestingly, the plasmatic levels were higher in the induction phase in paediatric patients than in adults.

Reliability of the estimation of systemic exposure in paediatric patients taking into account the inclusion of age in the population-PK model as a categorical covariate has been discussed by the Applicant. Age as a categorical Covariate was demonstrated to influence significantly the variability of Clearance and Volume of distribution. However, the effect of weight was identified as the most

significant covariate explaining the clearance of eculizumab since it resulted in the lowest ΔMOF (i.e., -79.343). Other alternative dosing scheme could have been tested in order to optimise the use of eculizumab in paediatric patients. It is acknowledged that a dose-response study might have helped in the selection of the optimal dose. Unfortunately this has not been done and no other doses have been tested in the studies conducted. Therefore, the question is whether the proposed dosing regimens can be accepted on the basis of their benefit/risk balance. The relatively high dose proposed in this indication may not be optimal particularly for long term side effects that could be avoided with a reduced posology. The applicant agreed to discuss the feasibility of a further study investigating efficacy and safety of lower doses at post-approval.

Data from paediatric population are scarce, due mainly to limited number of children recruited. In order to better characterise the PK profile and its relationship with efficacy and safety in this population, further evidence from the ongoing study should be provided in future updates. A controlled prospective study in paediatric aHUS patients is currently enrolling.

Regarding the analytical method, due to the issues detected with the one used in PNH, another method was developed to measure higher concentrations of eculizumab in aHUS patients. In spite of the limitation of the old method, it seems that the repercussion on the PK data is acceptable. In any case, the new method should be used in the ongoing trials, allowing a more reliable comparison between different samples and methods. Therefore, the applicant agreed to carry out all the analyses of the samples in the ongoing studies using the new analytical method. These results will be submitted in the next updates of the trials, comparing these results with PK data from studies C08-002, C08-003 and C09-001r.

A model for the mechanisms leading from impaired regulation of the alternative pathway to thrombotic microangiopathy has been described (Noris et al. in N Engl J Med 2009;361:1676-87).

3.3.3. Clinical efficacy

3.3.3.1. Dose response studies

No dose-response studies were submitted (see discussion on clinical pharmacology).

3.3.3.2. Main studies

Data from 67 patients in two prospective controlled studies and one retrospective study were used to evaluate the efficacy of eculizumab in the treatment of aHUS. The impact of chronic eculizumab treatment on the TMA process, TMA events, TMA interventions, kidney insufficiency, quality of life and anemia was examined. The two prospective clinical studies (C08-002A/B and C08-003A/B) were conducted in two distinct populations of aHUS patients with clinically different baseline characteristics and different expected clinical outcomes. Study C08-002A/B accrued patients in the early phase of aHUS with evidence of severe TMA manifestations with acute worsening of renal function. In these patients eculizumab is expected to control the TMA process, prevent further severe TMA manifestations, and reverse kidney damage.

Study C08-003A/B accrued patients with long term aHUS with apparent control of the TMA process due to chronic PT. Those patients had a long, sustained renal impairment prior to entering the trial. In this population eculizumab is expected to control the TMA process despite discontinuation of PT and also maintain kidney function.

Both studies were divided into Part A for adults and Part B for adolescents aged 12 to 18 years old. For both of the prospective studies, primary efficacy analyses are presented for the combined adult and adolescent cohorts.

Therefore, these studies are reported separately without integration in the efficacy analyses. In addition, the retrospective study (C09-001r) included a group of aHUS patients with multiple age categories and a wide range of disease history (see Table 6). These data were also reported separately without integration into the two prospective controlled clinical studies.

The prospective studies were designed for 26 weeks of eculizumab dosing with additional treatment available through the extension phase of each protocol. All patients included in the submission had a minimum of 26 weeks follow-up (unless they were discontinued early). Primary efficacy endpoints were assessed through week 26. The durability of effect was also assessed through data cut-off including the additional follow-up from the extension phase of the studies. Since the two prospective, controlled studies provided comparison to baseline, each patient was further used as an historical control in a time-matched analysis of specific measures of clinical efficacy.

The retrospective study provided safety and efficacy data especially with regard to paediatric aHUS patients.

Table 6: Tabular listing of clinical registration studies

Type of Study	Study Iden-tifier	Objective of Study	Study Design and Type of Control	Test Product: Dosage Regimen, Route of Administration	Number of Treated Patients	Diagnosis	Duration of Treatment	Study Status Type of Report
Phase 2	C08-002A/B	Assess the safety and efficacy of eculizumab in PT-resistant aHUS patients	Open label, single arm	Eculizumab : 900 mg IV once weekly (Weeks 1-4); followed by 1200 mg IV once every 2 weeks (week 5 and after)	17	aHUS	26 weeks; patients allowed to continue in extension until product registered and available (per country specific regulations)	Study completed, extension trial ongoing Data cut-off Sept 8, 2010
Phase 2	C08-003A/B	Assess the safety and efficacy of eculizumab in patients with aHUS treated chronically with PT	Open label, single arm	Eculizumab : 900 mg IV once weekly (Weeks 1-4); followed by 1200 mg IV once every 2 weeks (week 5 and after)	20	aHUS	26 weeks; patients allowed to continue in extension until product registered and available (per country specific regulations)	Study completed, extension trial ongoing Interim Study Report Data cut-off Oct 20, 2010
Retro-spective	C09-001r	Assess the efficacy and safety of eculizumab in aHUS patients treated outside of an Alexion-sponsored, clinical trial	Retrospective data collection via retrospective chart review	Adolescent and Adults same as above. Pediatric dosing in weight band	30	aHUS	Variable	Study completed

Source: Study C08-002A/BCSR, C08-003A/B CSR and C09-001r CSR

Two additional clinical studies in aHUS patients have been initiated: one in adult patients (C10-004) and one in paediatric patients (C10-003). Descriptions of these studies are provided in Table 7. At the time of the cut-off for this analysis (November 30, 2010) two patients were enrolled in the study C10-004 and none were enrolled in the study C10-003. These patients had minimal follow up and no data were available.

Table 7: Tabular listing of ongoing clinical studies

Type of Study	Study Identifier	Objective of Study	Study Design and Type of Control	Test Product: Dosage Regimen, Route of Administration	Number of Treated Patients	Diagnosis	Duration of Treatment	Study Status, Type of Report
Phase 2	C10-003	Assess safety and efficacy of eculizumab in pediatric aHUS patients	Open label, single arm	Eculizumab. Multiple weight-based dosing regimens.	0	aHUS	26 weeks; patients allowed to continue in extension until product registered and available (per country specific regulations	Ongoing; No analysis available
Phase 2	C10-004	Assess safety and efficacy of eculizumab in adult aHUS patients	Open label, single arm	Eculizumab : 900 mg IV once weekly (Weeks 1-4); followed by 1200 mg IV once every 2 weeks (week 5 and after)	2	aHUS	26 weeks; patients allowed to continue in extension until product registered and available (per country specific regulations	Ongoing; no analysis available

Cut-off date for this summary and enrollment: November 30, 2010

Study C08-002

Design

This was an open-label, non-randomised, single-arm multi-centre, controlled clinical trial of eculizumab in adults (≥18 years; protocol C08-002A) and adolescents (between ages from 12 and up to 18 years weighing ≥40 kg; protocol C08-002B) with PT-resistant aHUS (that is, aHUS patients who did not respond or insufficiently responded to, or were intolerant to aggressive PT), managed in 2 different protocols.

This was an open-label study and no prospective control groups were used. Each patient's historical experiences and data, collected during the pre-eculizumab treatment period, were used as comparators in several statistical analyses.

Study Participants

Main inclusion/exclusion criteria included:

1. Male or female patients ≥ 18 years (C08-002A) or between ages 12 and up to 18 years weighing ≥ 40 kg (C08-002B) and diagnosed with aHUS. Patients were either newly diagnosed, experienced a relapse of the disease, or had a post-transplant recurrence of the disease.
2. Exhibited a decrease in platelet count despite at least 4 PT treatments in the 1 week immediately prior to screening. At screening, platelet count must have been < 150 x 10^9/L and at least 25% lower than the average of 3 platelet counts obtained during the most recent TMA remission and at least 1 month apart during that remission prior to screening (designated the "average remission platelet count").
3. If historical counts were not available, platelet count at onset of the current aHUS exacerbation must be ≤ 75 x 10^9/L, and platelet count at screening must have been ≤ 100 x 10^9/L despite PT treatment administration of at least 4 PT treatments in the 1 week immediately prior to screening.

4. Known complement regulatory protein genetic abnormality, i.e., a mutation in Complement Protein 3, factor H or associated factor, factor I, MCP, known Factor B gain-of-function mutation, or known anti-CFH antibody ("aHUS lesions").

   Patients diagnosed with aHUS were eligible and were assigned to one of the following parallel categories during the treatment period of the trial:

   - Category 1: Factor H or Factor I functional deficiency, abnormal factor interaction (CFH/CFI FFP Group), or deletions of the CFHR1 and CFHR3 genes;
   - Category 2: Complement Protein 3, abnormal factor interaction (C3) or Factor B Gain of Function;
   - Category 3: Anti-CFH Antibody (Anti-CFH Group);
   - Category 4: MCP deficiency (MCP Group).

1. Patients diagnosed with aHUS without documented complement mutation or known anti-CFH antibody were eligible if other aetiologies of HUS were ruled out as confirmed in the Exclusion Criteria (i.e., including Shiga-toxin negative, non-infectious, non-drug exposure- related [i.e., cyclosporine]), no known human immunodeficiency virus (HIV) positivity, and anti-phospholipid antibody negative). Patients meeting these conditions were assigned to Category 5. In addition, these patients underwent genetic testing to determine if a mutation could be identified. If a mutation was identified, the patient was reassigned to the appropriate category.
2. Lactate dehydrogenase (LDH) level ≥ upper limit of normal (ULN) unless the patient was receiving PE and LDH at the onset of the current aHUS exacerbation was at least the ULN. If LDH was normal at screening, other markers indicative of ongoing haemolysis were evaluated, such as haptoglobin, schistocytes, and discussed with the Sponsor;
3. Creatinine level ≥ ULN for age (patients who required acute dialysis for acute renal failure were also eligible).
4. Typical HUS (known Shiga toxin +) (exclusion criteria)

Patients who experienced an aHUS exacerbation or disease progression during the study that, in the opinion of the investigator, required intervention with immunosuppressive therapies such as mTOR inhibitors or tacrolimus were to be discussed between the Investigator and the Sponsor for consideration of study discontinuation. If patients who were status post (s/p) kidney transplant and had developed AMR (C4d positive renal biopsy), and for whom Rituximab and/or IVIg were deemed the appropriate therapy, then these patients would have been required to withdraw from the study and receive standard of care therapy. Patients were also required to undergo the 8-week follow-up period after discontinuation of eculizumab therapy.

Treatments

Patients received the first dose of eculizumab between 1 and 6 hours after the completion of the PT session administered closest to the point in time eligibility was confirmed (known as the Qualifying PT Episode).

Eculizumab 600 mg, 900 mg or 1200 mg was administered intravenously according to the following regimens:

- Induction Period: patients received eculizumab 900 mg via IV infusion over approximately 35 minutes once a week (every 7 ± 2 days) for four weeks.

- Week 5: patients received 1200 mg eculizumab via IV infusion over approximately 35 minutes for the 5th dose (7 ± 2 days after 4th dose).
- Maintenance Period: after the fifth dose, patients received eculizumab 1200 mg via IV infusion over approximately 35 minutes every two weeks (every 14 ± 2 days).

If the physician administered PPH, PE, or FFP, 600 mg eculizumab was to be administered (i) within 60 minutes after each PPH or PE and (ii) within 60 minutes prior to each 2 units of FFP infusion, respectively.

The Treatment Period commenced with the first eculizumab dose. The first 26 weeks of treatment defined the time period for assessments of the endpoints. Additionally, when available, all data collected in the extension period were also included in the assessment of efficacy and safety endpoints (up to data cut-off date), as detailed in the final SAP, Amendment 1. Patients were allowed to continue to receive eculizumab treatment until the product was registered and available to treat patients diagnosed with aHUS (in accordance with country specific regulation).

The treatment with IVIg and Rituximab were prohibited during the study:

Patients previously treated with IVIg were required to have an 8-week washout period and patients previously treated with Rituximab were required to have a 12-week washout period prior to being enrolled in this study.

If patients who were status post kidney transplant had developed AMR (C4d positive renal biopsy), and for whom Rituximab was deemed the appropriate therapy, then these patients would have been required to withdraw from the study and receive standard of care therapy.

The following concomitant medications and therapy during the study were allowed under certain circumstances and restrictions:

- Patients receiving other immunosuppressive therapies such as steroids, calcineurin inhibitors (mTOR) inhibitors or tacrolimus were allowed under the following circumstances ONLY IF: (1) part of an established post-transplant anti-rejection regime and dose of such medications must have been unchanged for at least four weeks prior to screening, or (2) patient confirmed anti-CFH antibody requiring immunosuppressive therapy and dose of such medications must have been unchanged for at least four weeks prior to screening or (3) patient experienced an acute aHUS relapse immediately after transplant. In addition, a stable dose of these medications was to be maintained during the Treatment Period unless there was a discussion and agreement between the Investigator and the Sponsor.
- Patients receiving ESAs were allowed if the patient had been on a stable dose for at least four weeks prior to screening, or a washout period of at least 2 weeks from the last dose of ESA therapy. In addition, a stable dose of these medications must have been maintained during the Treatment Period unless there was a discussion and agreement between the Investigator and the Sponsor.
- Use of any other investigational drug or device was prohibited beginning four weeks prior to screening and throughout the entire trial

After entry into the trial, patients were not permitted to receive PT within the first 96-hour period following the first eculizumab dose or new dialysis within the first 48-hour period following the first eculizumab dose unless there was compelling medical need. Exceptions to the rescue criteria were to be approved prior to administration on a case-by-case basis by the Sponsor.

Objectives

The primary objective of the study (per protocol) was to assess the effect of eculizumab to reduce TMA as measured by platelet count change from baseline during the eculizumab treatment period to the first 26 weeks in patients with PT-resistant aHUS, including assessment of the proportion of patients who experience platelet count normalization from baseline through 26 weeks as well as through data cut-off date.

If the protocol specified primary endpoint of platelet change from baseline was statistically significant, another primary objective was to estimate the proportion of patients who achieved Haematologic Normalization from baseline through 26 weeks as well as to the data cut-off date.

Statistical Methods and Sample size

The ITT population was defined as all patients who received any amount of eculizumab, and were considered evaluable for safety and efficacy analyses. The first dose of eculizumab in the Treatment Period was considered as study Day 0. The study day was presented and calculated relative to the first dosing day.

For all efficacy endpoints, the primary analysis was based on the ITT population, and missing data was imputed; additional details are provided in the final SAP Amendment 1 (Appendix 16.1.9). The last patient data recorded for this interim report occurred on or before September 8, 2010, which afforded a minimum of 26 weeks in the Treatment Period for all patients who continued in the study.

The main analysis for this study was based on the pooled data of the two protocols for adult patients (C08-002A) and a similar protocol for adolescent patients (C08-002B).

With at least 12 patients enrolled between the two protocols and assuming a null hypothesis of no post-dose change from baseline in mean platelet count, the study had approximately 88% power to detect as statistically significant an effect size (mean change from baseline / standard deviation) of at least 1 when using a one sample t-test with a two-sided $\alpha = 0.05$. Up to approximately 15 patients were to be enrolled between the protocol of adult patients (C08-002A) and the protocol of adolescent patients (C08-002B).

Efficacy endpoints

- Platelet Count Change from Baseline and Platelet Count Normalization

  Platelet count change from baseline (Platelet Count Pre-PT baseline Set-point value) at each post-dose day of measurement (excluding days 1 to 4) to the first 26 weeks of treatment was assessed using a repeated measurement analysis of variance (ANOVA) model. Statistical significance of a positive or negative increase in the change from baseline was assessed at the 5% level at each time point.

  The proportion of patients who experienced platelet count normalisation (protocol defined secondary endpoint of TMA remission rate) was assessed from baseline through 26 weeks as well as through data cut-off date. This was reported for the entire population and for patients with abnormal baseline platelet count ($<150 \times 10^9$/L).

- Haematologic Normalisation

  Haematologic Normalisation was defined as normalisation of both platelet count and LDH sustained for at least two consecutive measurements which span a period of at least four weeks. Counts and proportions were produced for the patients in a state of Haematologic Normalisation at each day starting from week four after the first eculizumab dose. This analysis was performed for all patients

as well as for the subgroups defined by presence or absence of identified complement regulatory factor mutations. Exact binomial CIs were produced for the analysis which combines all patients into a single group.

The time to Haematologic Normalisation was calculated from Day 0 until the two components of Haematologic Normalisation had met the conditions which lead to the confirmation of Haematologic Normalisation. For example, platelet count may already have been ≥150 x 10^9/L and LDH was just starting to decrease to ≤ULN [i.e., the first of two consecutive normal measurements which span a period of at least four weeks]). The CDF of the time to Hematologic Normalization was also generated. The time represented on the CDF plot represented target windows.

The duration of Haematologic Normalisation was based on the longest interval in days between the time of occurrence and the last response day or study day (data cut-off date) in which the patient was in the state of haematologic normalization. The last response day was the day when the patient no longer met criteria for hematologic normalization. The survival plot of the duration of Haematologic Normalization was generated excluding those patients who did not achieve Haematologic Normalization during the study (responders only). The time presented on the survival plot represents two-week interval.

- Secondary endpoints:

Evaluate additional endpoints from baseline through 26 weeks and/or from baseline through data cut-off date, including the last visit for early termination, such as the effect of eculizumab on:

- TMA Intervention Rate (# PT and # Dialysis Events/Patient/Day) in the eculizumab treatment period (from baseline through 26 weeks and through data cut-off date) compared with the TMA Intervention Rate during the pre-eculizumab treatment period.

- TMA Event-Free status defined as the absence for at least 12 weeks of (1) decrease in platelet count of >25% from the Platelet Count Pre-PT Baseline Set-Point; (2) PT while the patient is receiving eculizumab, and (3) new dialysis.

- Quality of Life measures.

- Renal function measures.

- Hemoglobin (at least 20 g/L)

- Complete TMA Response (analysis requested by the regulatory authorities.). Complete TMA Response was defined as Haematologic Normalization plus improvement in renal function (25% reduction from baseline in serum creatinine, which was sustained for two consecutive measurements which span a period of at least four weeks)

- Characterize the overall safety and tolerability of eculizumab.

- Describe the pharmacokinetic (PK) and pharmacodynamic (PD) properties of eculizumab in patients with aHUS

Results
Participant flow

There were a total of 17 patients enrolled between the protocol for adult patients (C08-002A, 16 adult patients enrolled) and the separate protocol for adolescent patients (C08-002B, one adolescent patient enrolled). For efficacy and safety analyses, all 17 patients were included in the ITT population. At the time of data cut-off date, 4 of 17 patients (24%) were no longer on eculizumab treatment. Two

patients completed the 26-week treatment period, but did not continue in the extension period. One patient discontinued from the study 6 weeks from the first eculizumab dose due to adverse events which were not related to eculizumab. One patient was discontinued due to a protocol violation (was diagnosed with SLE one week following dosing with eculizumab). Thus, a total of 13 (76%) patients continued into the extension treatment period.

Observations collected from the 8-week follow-up for the two patients who discontinued early and one of the two patients who did not continue in the extension treatment period showed that, at data cut-off date, 1 of these 3 patients (33%) who were no longer on study drug, had an ongoing aHUS exacerbation post-transplant prior to study enrolment. One of the two patients who did not continue in the extension period, data were not collected during the 8-week follow-up period as the patient refused to continue participation in the study.

Table 8: Patient disposition

Characteristic	Total (N=17) n (%)
Enrolled	17 (100)
Treated	17 (100)
Status at Data cut-off date	
Off Eculizumab	4 (24)
On Eculizumab	13 (76)
Reason Off Eculizumab	
Adverse event	1 (6)
Completed treatment period, is not continuing in the extension period	2 (12)
Protocol violation	1 (6)

Conduct of the study

The original protocol for Study C08-002A/B was finalized on 05 Nov 2008 and was subsequently amended four times:

Key changes from the initial Protocol C08-002A/B included:

- Changes in the inclusion/exclusion criteria
- Inclusion of additional efficacy endpoints
- Change from PP analysis to ITT analysis
- Analysis based on the adolescents and the adult protocols alone were not performed
- Changes to the Planned Analyses as Described in the Final SAP

Baseline demographics

Table 9: Patient demographic characteristics

Characteristic	Summary Statistics (N=17)
Age at Visit 1 (years)	
Median (Min; Max)	28 (17; 68)
Population Age Category [n(%)]	
Adolescent (12 to <18 years)	1 (6)
Adult (≥18 years)	16 (94)
Sex [n(%)]	
Female	12 (71)
Male	5 (29)
Proportion of Patients with Any Complement Regulatory Factor Mutation or Auto-Antibody Identified [n (%)]	13 (76)
Proportion of Patients with One Mutation	9 (53)
Proportion of Patients with Multiple Mutations	4 (24)
Type of Mutation [n (%)]:	
Anti-Factor H Antibody Titer, Factor CFHR3-CFHR1 – Mutation	1 (6)
C3 – Mutation	1 (6)
CD46 (MCP) – Mutation	1 (6)
CFHR1, CFHR3- Mutations, Anti-Factor H	1 (6)
Factor H- Mutation	4 (24)
Factor H- Mutation, CFHR1- Mutation, CFHR3- Mutation	1 (6)
Factor H- Mutation, Factor I- Mutation, CFHR3-CFHR1 - Mutation	1 (6)
Factor I- mutation	3 (18)

Baseline disease characteristics

All patients initiated treatment rapidly after the aHUS exacerbation leading up to eculizumab therapy. Patients were experiencing the current aHUS exacerbation for a median (min; max) of 0.75 (0.23; 3.70) months prior to screening (Table 10). Seven patients (41%) had a history of kidney transplant. No patient had a history of nephrectomy. Seven patients (41%) were experiencing their first presentation of aHUS.

Table 10: Summary of patient aHUS disease history

Characteristic	Summary Statistics (N=17)
Time from aHUS diagnosis to screening (month)[a]	
Mean (SD)	41.4 (68.1)
Median (Min; Max)	9.70 (0.26; 236)
Proportion of patients with prior renal transplant [n (%)]	7 (41)
First presentation of aHUS [n (%)]	7 (41)

As noted in Table 11, the median time from the aHUS diagnosis to screening that led to enrollment in the study was 9.70 months (min;max: 0.26; 236 months). Thus, the majority of patients were receiving PT for an extended period of time for their aHUS exacerbation. Patients received an average of 5 ± 2 PT sessions in the 7 days prior to the first dose of eculizumab. All but one patient had at least 4 PT sessions in the week prior to screening. One patient had to discontinue PT after 2 sessions because of intolerance to PT (allergic reaction) and had no PT in the 7 days prior to eculizumab. Six patients (35%) required dialysis within 56 days of the first dose of eculizumab

Table 11: Summary of patient current aHUS exacerbation history

Characteristic	Summary Statistics (N=17)
Time from Current Exacerbation until Screening (Months)[a]	
N (patients)	17
Mean (SD)	1.10 (1.05)
Median (Min; Max)	0.75 (0.23; 3.70)
Number of PT sessions during current exacerbation	
Mean (SD)	17.1 (10.4)
Median (Min; Max)	17 (2; 37)
Number of PT sessions within 7 days prior to first eculizumab dose[b,c]	
Mean (SD)	5.41 (2.00)
Median (Min; Max)	6 (0;7)
Proportion of patients with dialysis within 56 days of the first dose of eculizumab [n (%)]	6 (35)

[a] Time from current exacerbation until screening = (screening date - date of current aHUS + 1) / 30.5
[b] Patient [redacted] did not receive PT 7 days prior to first dose due to allergic reaction
[c] Only sessions associated with current exacerbations were counted.
Source: Table 14.1.5

Table 12: Baseline characteristics

Characteristic	Summary Statistics (N=17)
Platelet Count ($x10^9$/L)	
Mean (SD)	109 (32.1)
Median (Min; Max)	118 (62; 161)
Number of patients [n (%)] in respective platelet Category	
< 150 $x10^9$/L	15 (88)
≥ 150 $x10^9$/L	2 (12)
LDH (U/L)	
Mean (SD)	323 (138)
Median (Min; Max)	269 (134; 634)
Number of patients [n (%)]in respective LDH Category	
≤ ULN	7 (41)
> ULN	10 (59)
Creatinine (µmol/L)	
Mean (SD)	352 (215)
Median (Min; Max)	256 (124; 787)
Number of patients [n(%)] with eGFR (mL/min/1.73*m^2) categorized as follows	
<15	7 (41)
15-29	5 (29)
30-44	4 (24)
45-59	1 (6)
60-89	0 (0)
> 90	0 (0)
Number of patients [n (%)] within each CKD Stage	
Stage 0	0 (0)
Stage 1	0 (0)
Stage 2	0 (0)
Stage 3a	1 (6)
Stage 3b	4 (24)
Stage 4	5 (29)
Stage 5	7 (41)

Primary endpoint:

1. Platelet Count Change from Baseline and Platelet Count Normalisation

The ANOVA of change from baseline platelet count at each post-dose day of measurement demonstrated a statistically significant (P <0.05) increase in platelet count as early as Day 7 and through 26 weeks (except Day 21). The point estimate change from baseline through 26 weeks was 72.7 x 10^9/L (95% CI: 40.1-105.2; P=0.0001) (Table 13).

Table 13: Change from baseline in platelet count (x10^9/L)

Time Post-Dose	N	Point Estimate	*P*-value
Day 7	17	42.2	0.0271
Through Week 26	15	72.7	0.0001

Results of platelet count normalisation and the proportion of patients achieving first occurrence of normal platelet count (≥150 x 10^9/L) from baseline through 26 weeks compared with those from baseline through data cut-off date were identical.

Overall, platelet counts increased and were within normal limits in 14 of 17 patients (82%; 95% CI: 57%-96%) during the eculizumab treatment period. As of the data cut-off date, the time to first occurrence of normal platelet count (≥ 150 x 10^9/L) occurred as early as one day following the first eculizumab dose, with a median time of 7 days to achieve a first occurrence of platelet count normalisation (Figure 1).

Two of the 17 patients enrolled in this study had a platelet count ≥150 x 10^9/L at baseline. Of the 15 patients with abnormal platelet count at baseline, 13 patients (87%) achieved platelet count normalisation (Table 14). Among patients with normalization of platelet count, the maximum duration of platelet count normalisation ranged from 14 to 64 weeks (98 to 448 days) after the first eculizumab dose, as of the data cut-off date (Figure 1).

Table 14: Platelet count normalisation and first occurrence of normal platelet count from baseline through data cut-off date

	Number of Patients with Improvement/Total patients (%)		
	Platelet Count at Baseline		All Patients (N=17)
	<150 x 10^9/L (n=15)	≥150 x 10^9/L (n=2)	
Platelet Count Normalization[a] from baseline through data cut-off date	13/15 (87)	1/2 (50)	14/17 (82)
At least One Platelet Count ≥150 x 10^9/L from baseline through data cut-off date	14/15 (93)	2/2 (100)	16/17 (94)

[a]Platelet count being observed to be ≥ 150 x 10^9/L on at least two consecutive measurements which span a period of at least four weeks.

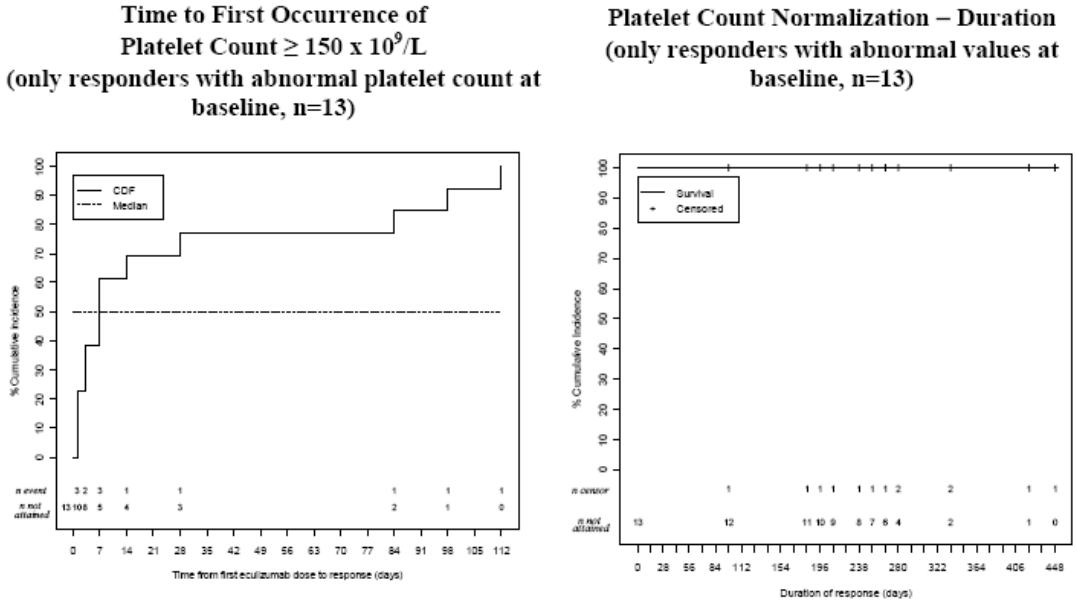


Figure 1: Platelet count > 150 x 10^9/L – Time to first occurrence

2. Haematologic Normalisation

Haematologic Normalisation was achieved in the majority of patients. Overall, 13 of 17 patients (76%) achieved Haematologic Normalisation (95% CI: 50%-93%) (Table 15). Of the 10 patients with both abnormal platelet count and LDH at entry, 9 patients (90%) achieved Haematologic Normalisation. A similar proportion of patients achieved Haematologic Normalisation with or without identified complement regulatory factor mutations or auto-antibodies.

Table 15: Haematologic normalisation from baseline through data cut-off date

	Number of Patients with Improvement/Total patients (%)	n	Maximum Duration (Days)
All patients (N=17)	13/17 (76)	13	258 (175; 431)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=13)	10/13 (77)	10	263 (175; 431)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=4)	3/4 (75)	3	237 (196; 285)

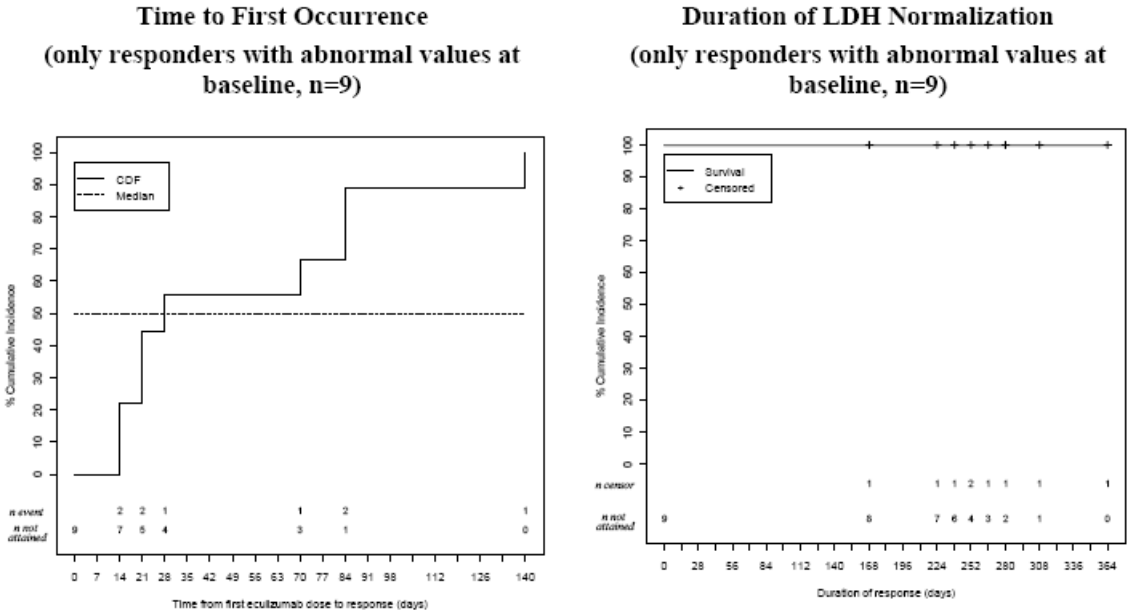


Figure 2: Normal LDH (≤ULN) - Time to first occurrence and duration

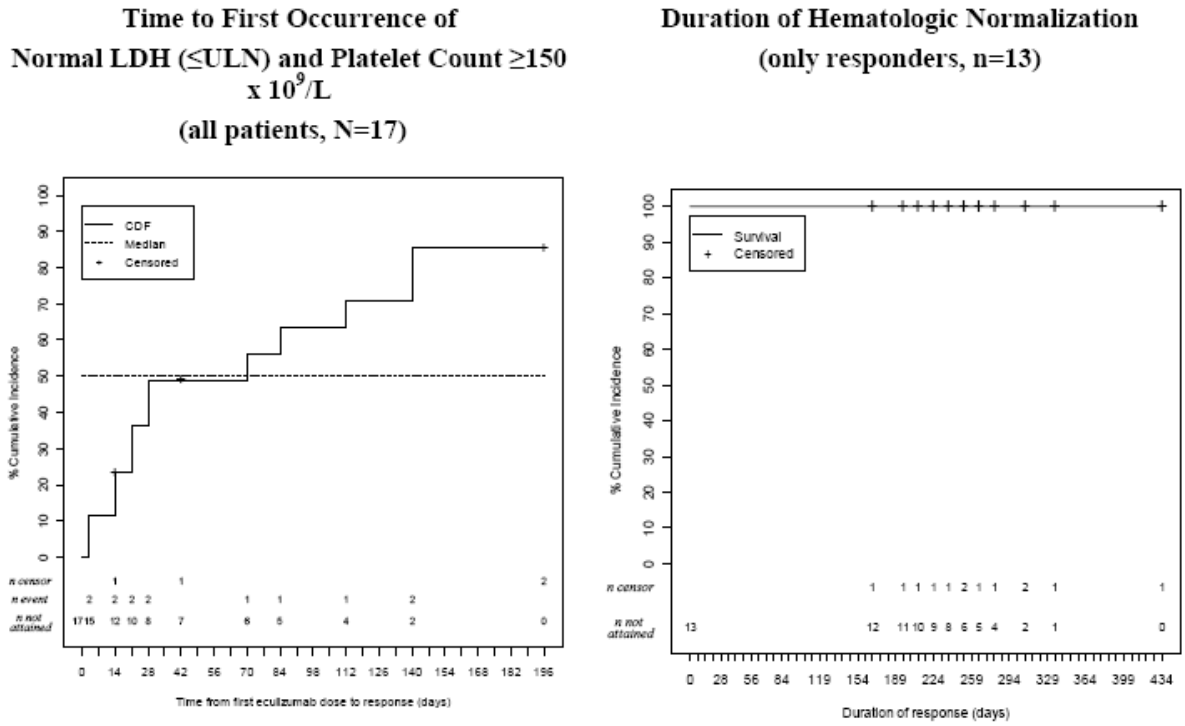


Figure 3: Haematologic normalisation - Time to first occurrence and duration

TMA Intervention Rate

TMA Intervention rate improved from a median of 0.88 events/patient/day to 0 events/patient per day through 26 weeks and through data cut-off.

Table 16: TMA intervention rates pre-eculizumab treatment and during eculizumab treatment from baseline through data cut-off date

TMA Intervention	Pre-Eculizumab Treatment (N=17)[a]	During Eculizumab Treatment (N=17)[b]	*P*-value (Signed-Rank)
Intervention rate per patient (PT sessions plus dialysis/patient/day) Median (Min; Max)	0.88 (0.04; 1.59)	0 (0.00; 0.31)	< 0.0001
Number of patients (% of Total) with a dialysis event (pre-eculizumab treatment) or new dialysis[c] (during eculizumab treatment)	6 (35)	1 (6)	N/A
Number of patients (% of Total) receiving Plasma Therapy[d]	17 (100)	2 (12)	N/A
Number of Plasma therapies Median (Min; Max)	13 (2; 37)	0 (0; 20)	N/A

N/A: Not applicable.
[a] from the later of (1) the start of the current aHUS episode or (2) eight weeks prior to first eculizumab dose until the first eculizumab dose
[b] from the first eculizumab dose to the earlier of (1) the last visit or (2) data cut-off date
[c] Only dialysis occurring on or after 15 days following the first dose are counted in the during treatment period.
[d] Patient 2-043-01 received plasma therapy during the post-discontinuation follow-up period.

TMA Event-Free Status

15 patients (88%) achieved TMA Event-Free status, a key secondary endpoint. As of the data cut-off date, the median time to attain TMA Event-Free status was 12 weeks. The maximum length of TMA Event-Free status was sustained for a median duration of 38 weeks (14 to 64 weeks).

Table 17: Summary of TMA event-free status from baseline through data cut-off date

	Number of Patients with Improvement/Total patients (%)	Maximum Duration (Days)	
		n	Median (Min;Max)
All patients (N=17)	15/17 (88)	15	264 (98; 448)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=13)	12/13 (92)	12	271 (98; 448)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=4)	3/4 (75)	3	264 (223; 367)

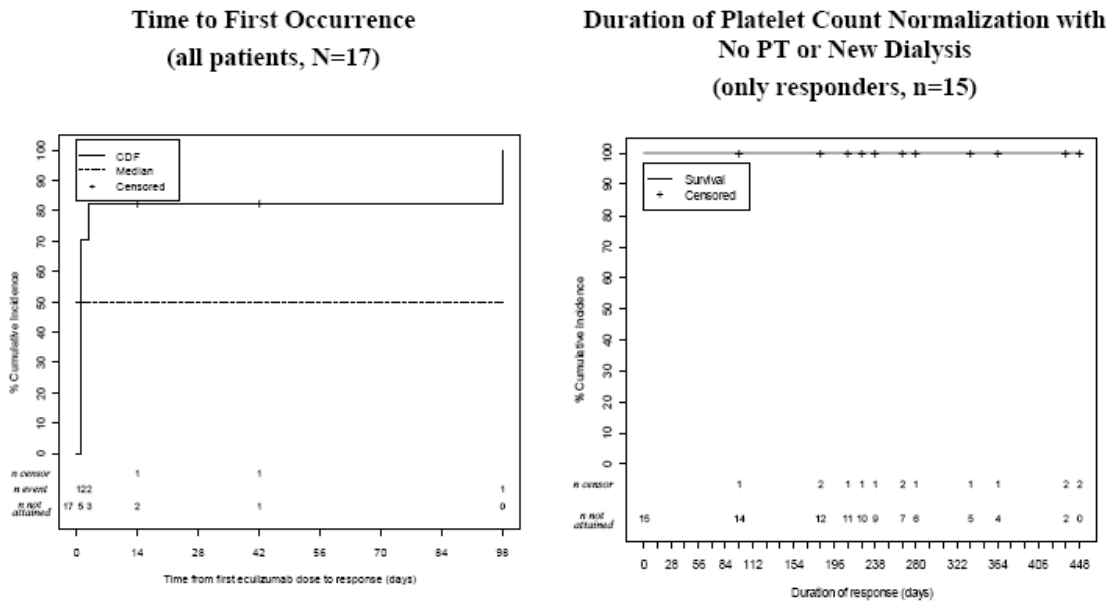


Figure 5: TMA event-free status - Time to first occurrence and duration

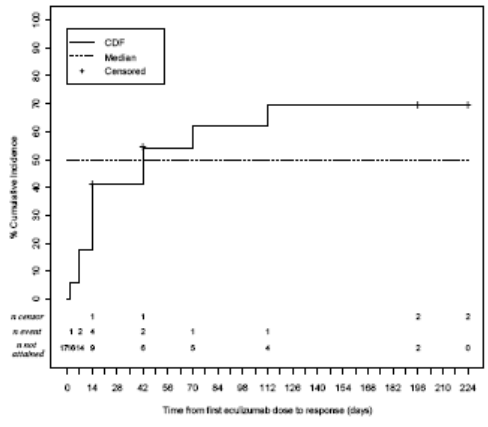
Change in Renal Function Parameters

Table 18: Proportions of patients with improvement in renal function from baseline through data cut-off date

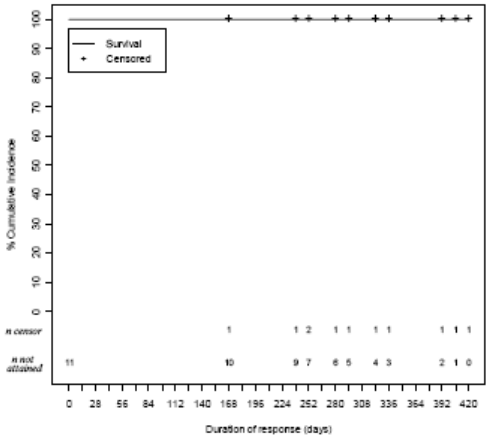
	Number of Patients with Improvement/Total patients (%)	
	At Least One Measurement Demonstrating Improvement	Sustained[a]
eGFR improvement ≥15mL/min/1.73 m^2		
All patients (N=17)	11/17 (65)	9/17 (53)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=13)	9/13 (69)	7/13 (54)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=4)	2/4 (50)	2/4 (50)
Improvement in at Least One CKD Stage[b]		
All patients (N=17)	13/17 (76)	10/17 (59)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=13)	11/13 (85)	8/13 (62)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=4)	2/4 (50)	2/4 (50)
Creatinine Decrease of at Least 25% from Baseline		
All patients (N=17)	14/17 (82)	11/17 (65)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=13)	12/13 (92)	9/13 (69)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=4)	2/4 (50)	2/4 (50)

[a] Sustained is defined as two consecutive visits spanning at least four weeks
[b] CKD: Including Stages 1, 2, 3a, 3b, 4 and 5

Time to First Occurrence
(all patients, N=17)



Duration
(only responders, n=11)



Note: The responders with Time 2, 3 days were grouped in target windows around 7 days.

Figure 6: Decrease of creatinine ≥25% from baseline - Time to first occurrence and duration

Complete TMA Response

Table 19: Complete TMA response from baseline through data cut-off date

	Number of Patients with Improvement/Total patients (%)	n	Maximum Duration (Days)
All patients (N=17)	11/17 (65)	11	267 (175; 389)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=13)	9/13 (69)	9	267 (175; 389)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=4)	2/4 (50)	2	261 (237; 285)

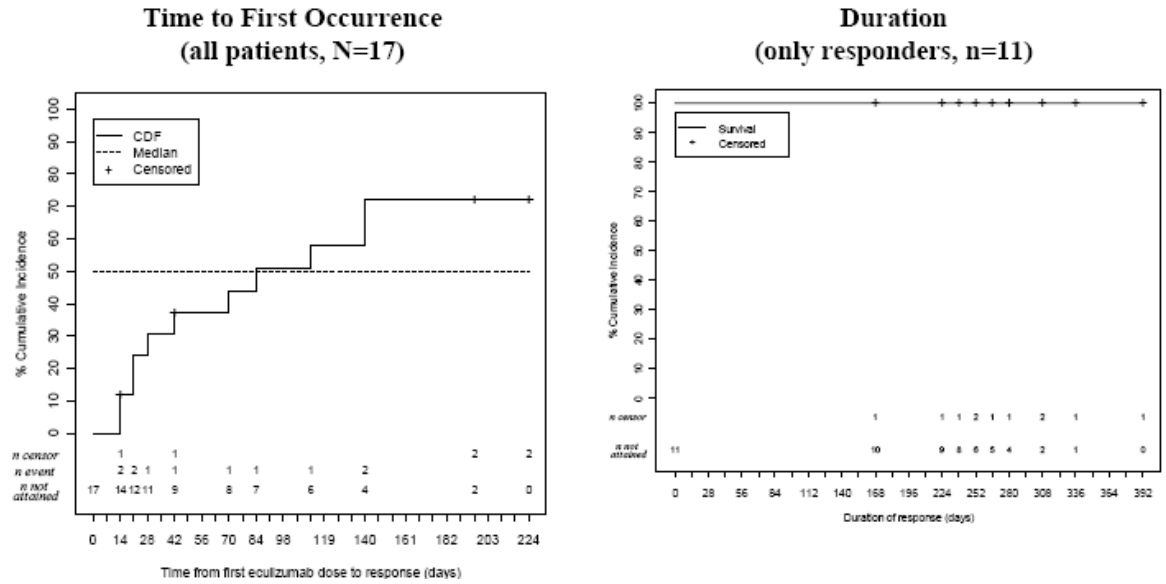


Figure 7: Complete TMA response- Time to first occurrence and duration

Change in Haemoglobin

Table 20: Improvement in haemoglobin levels from baseline through data cut-off date

	Number of Patients with Improvement/Total patients (%)	
	At Least One Measurement Demonstrating Improvement	Sustained[a]
All patients (N=17)	12/17 (71)	12/17 (71)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=13)	10/13 (77)	10/13 (77)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=4)	2/4 (50)	2/4 (50)

[a] Sustained is defined as two consecutive visits spanning at least four weeks

Source: Table 14.3.6.3a

Quality of life

A large proportion of patients (80% through 26 weeks and 87% through data cut-off) achieved an MID of 0.06 in the EuroQol 5D measurements, which did not seem to be affected by complement regulatory factor mutation status. Similar results were obtained with the VAS index scores, with both test results reflecting a positive improvement in health outcome and quality of life of the study patients.

Subgroups analyses

Analyses of patient subgroups for the presence of complement regulatory factor mutations, duration of plasma therapy, dialysis, first clinical manifestation of TMA, age, sex, and race indicate that generally similar benefits were observed with eculizumab treatment in regard to the specific variables assessed within these subgroups including change in platelet count, TMA event free status, hematologic normalization, complete TMA response, change in eGFR ≥15 mL/min/ 1.73 m^2, and change in hemoglobin.

One important subgroup is the cohort of patients with a history of kidney transplant. Patients with and without prior kidney transplant have a similar response to eculizumab treatment with regard to change in platelet count, TMA event free status, hematologic normalization, and change in hemoglobin. Patients with a prior kidney transplant may be less likely to demonstrate a clinically meaningful improvement in kidney function compared to patients without a prior history of kidney transplant. Only 1 of 7 (14%) patients with a history of kidney transplant improve their renal function by at least 15 mL/min/1.73 m^2 compared to 7/10 (70%) patients without a history of transplant and 8/17 (47%) patients in the entire study population. Patients who have previously undergone kidney transplant, and thus are reduced to depending on only a single functioning kidney, may be more vulnerable to the post transplant TMA insult and therefore less able to experience a recovery in renal function when eculizumab is commenced following intensive PT as compared to patients with two functioning kidneys.

Study C08-003A/B

Design

This was an open-label, non-randomized, single-arm, multi-centre, controlled clinical trial of eculizumab in adults (≥ 18 years; Protocol C08-003A) and adolescents (between ages from 12 and up to 18 years weighing ≥ 40 kg; Protocol C08-003B) with aHUS receiving chronic PT.

This study was an open-label study and no prospective control groups were used. Each patient's historical experiences and data collected during the Observation Period were used as comparators in several statistical analyses

Study Participants

Main inclusion/exclusion criteria included:

1. Male or female patients ≥ 18 years (C08-003A) or between ages 12 and up to 18 years weighing ≥ 40 kg (C08-003B) and who have been diagnosed with aHUS..
2. Patients must have been receiving PT for aHUS and must have been observed to receive ≥ 1 PT treatment every two weeks and no more than 3 PT treatments/week (at an unchanged frequency) for at least 8 weeks before the first dose of eculizumab.
3. Platelet Count Pre-PT Baseline Set-Point (collected in the hours before the Qualifying PT Episode) was within 75% of the average of the Pre-PT platelet counts collected at screening and during the Observation Period.
4. Known complement regulatory protein genetic abnormality, i.e., a mutation in Complement Protein 3, factor H or associated factor, factor I, MCP, known Factor B gain-of-function mutation, or known anti-CFH antibody ("aHUS lesions").

   Patients diagnosed with aHUS were eligible and were assigned to one of the following parallel categories during the treatment period of the trial:

   - Category 1: Factor H or Factor I functional deficiency, abnormal factor interaction (CFH/CFI FFP Group), or deletions of the CFHR1 and CFHR3 genes;
   - Category 2: Complement Protein 3, abnormal factor interaction (C3) or Factor B Gain of Function;
   - Category 3: Anti-CFH Antibody (Anti-CFH Group);
   - Category 4: MCP deficiency (MCP Group).

1. Patients diagnosed with aHUS without documented complement mutation or known anti-CFH antibody were eligible if other etiologies of HUS were ruled out as confirmed in the Exclusion Criteria (i.e., including Shiga-toxin negative, non-infectious, non-drugexposure- related [i.e., cyclosporine]), no known human immunodeficiency virus (HIV) positivity, and anti-phospholipid antibody negative). Patients meeting these conditions were assigned to Category 5. In addition, these patients underwent genetic testing to determine if a mutation could be identified. If a mutation was identified, the patient was reassigned to the appropriate category.
2. Lactate dehydrogenase (LDH) level ≥ upper limit of normal (ULN) unless the patient was receiving PE and LDH at the onset of the current aHUS exacerbation was at least the ULN. If LDH was normal at screening, other markers indicative of ongoing hemolysis were evaluated, such as haptoglobin, schistocytes, and discussed with the Sponsor;
3. Creatinine level ≥ ULN for age (patients who required acute dialysis for acute renal failure were also eligible).
4. Typical HUS (known Shiga toxin +) (exclusion criteria)

Patients who experienced an aHUS exacerbation or disease progression during the study that, in the opinion of the investigator, required intervention with immunosuppressive therapies such as mTOR inhibitors or tacrolimus were to be discussed between the Investigator and the Sponsor for consideration of study discontinuation. If patients who were status post (s/p) kidney transplant and had developed AMR (C4d positive renal biopsy), and for whom Rituximab and/or IVIg were deemed the appropriate therapy, then these patients would have been required to withdraw from the study and receive standard of care therapy. Patients were also required to undergo the 8-week follow-up period after discontinuation of eculizumab therapy.

Treatments

Patients received the first dose of eculizumab between 1 and 6 hours after the completion of the PT session administered closest to the point in time eligibility was confirmed (known as the Qualifying PT Episode).

Eculizumab 600 mg, 900 mg or 1200 mg was administered intravenously according to the following regimens:

- Induction Period: patients received eculizumab 900 mg via IV infusion over approximately 35 minutes once a week (every 7 ± 2 days) for four weeks.
- Week 5: patients received 1200 mg eculizumab via IV infusion over approximately 35 minutes for the 5th dose (7 ± 2 days after 4th dose).
- Maintenance Period: after the fifth dose, patients received eculizumab 1200 mg via IV infusion over approximately 35 minutes every two weeks (every 14 ± 2 days).

If the physician administered PPH, PE, or FFP, 600 mg eculizumab was to be administered (i) within 60 minutes after each PPH or PE and (ii) within 60 minutes prior to each 2 units of FFP infusion, respectively.

The Treatment Period commenced with the first eculizumab dose. The first 26 weeks of treatment defined the time period for assessments of the endpoints. Additionally, when available, all data collected in the extension period were also included in the assessment of efficacy and safety endpoints (up to data cut-off date), as detailed in the final SAP, Amendment 1. Patients were allowed to continue

to receive eculizumab treatment until the product was registered and available to treat patients diagnosed with aHUS (in accordance with country specific regulation).

The treatment with IVIg and Rituximab were prohibited during the study:

Patients previously treated with IVIg were required to have an 8-week washout period and patients previously treated with Rituximab were required to have a 12-week washout period prior to being enrolled in this study.

Patients who were status post kidney transplant who newly developed antibody mediated rejection (AMR) (C4d positive renal biopsy) and for whom Rituximab was deemed the appropriate therapy were required to withdraw from the study and received standard of care therapy.

The following concomitant medications and therapy during the study were allowed under certain circumstances and restrictions:

- Patients receiving other immunosuppressive therapies such as steroids, mTOR inhibitors or tacrolimus were allowed to participate in the study under the following circumstances: [1] therapies were part of an established post-transplant anti-rejection regime and dose of such medications were unchanged for at least 4 weeks prior to screening, or [2] patient had confirmed anti-CFH antibody requiring immunosuppressive therapy and dose of such medications must have been unchanged for at least 4 weeks prior to screening and throughout the Observation Period or [3] patient was experiencing an acute aHUS relapse immediately after transplant. In addition, a stable dose of these medications was maintained during the Treatment Period unless there was a discussion and agreement between the Investigator and the Sponsor.
- Patients receiving erythrocyte stimulating agents (ESAs) were allowed to participate in the study if the patient had been on a stable dose for at least 4 weeks prior to screening and throughout the Observation Period, or a washout period of at least 2 weeks after the last dose of ESA therapy. In addition, a stable dose of these medications must have been maintained during the Treatment Period unless there was a discussion and agreement between the Investigator and the Sponsor
- Use of any other investigational drug or device was prohibited beginning four weeks prior to screening and throughout the entire trial

After entry into the trial, patients were not permitted to receive PT during the time intervals specified in Table 21 (based on the Pre-Treatment PT Regimen), nor were they permitted to receive new dialysis within the first 48-hour period following the first eculizumab dose unless there was compelling medical need, as assessed by (i) a new decrease in platelet counts > 25% below the Platelet Count Pre-PT Baseline Set-point value and to a level less than 150 x 10^9/L; or (ii) a new decrease in platelet count below 40 x 10^9/L; or (iii) an emergent and new neurological, renal, or other clinical event as prospectively defined for each patient. If one of these conditions applied, then the physician may have, at his or her discretion, instituted PT sessions based on the clinical assessment of the patient and after discussion with the Sponsor. If the physician administered PPH, PE, or FFP, 600 mg eculizumab must have been administered (i) within 60 minutes after each PPH or PE and (ii) within 60 minutes prior to each 2 units of FFP infusion, respectively.

Patients who required chronic dialysis prior to entry into the study may have continued this treatment throughout the 48-hour period following the first dose of eculizumab. Exceptions to the rescue criteria were to be reviewed with the Sponsor on a case-by-case basis prior to administration on a case-by-case basis by the Sponsor.

Table 21: Plasma therapy as rescue therapy

Pre-Treatment PT Regimen	Rescue PT Regimen
One PT per week	No PT therapy within first 2 weeks following first eculizumab dose
Two PTs per week	No PT therapy within first 1 week following first eculizumab dose
Three PTs per week	No PT therapy within first 96 hours following first eculizumab dose

Patients were not permitted to receive PT after the first eculizumab dose unless there was a compelling medical need.

During the treatment period, PT was administered in response to a confirmed decrease in platelet count of > 25% from the Platelet Count Pre-PT Baseline Set-Point value and a platelet count <150 x 10^9/L.

If, at any time during the treatment period, platelet counts decreased below 40 x 10^9/L and/or new neurological, renal, or other clinical signs arose as prospectively defined for each patient, PT may have been administered at the Investigator's discretion to maintain a platelet count above the Platelet Count Pre-PT Baseline Set-Point utilizing the same regimen employed prior to initiation of eculizumab therapy.

Patients were not permitted to receive new dialysis within the first 48-hour period following the first dose of eculizumab unless there was compelling medical need as assessed by (i) hypervolemia unresponsive to diuretics (ii) refractory electrolyte imbalance, or (iii) new-onset uremic encephalopathy, and after discussion with the Sponsor. Patients who required chronic dialysis prior to entry into the study may have continued this treatment throughout the 48-hour period following the first dose of eculizumab.

Objectives

The primary objectives of this study were to:

- Assess the effect of eculizumab on TMA Event-Free status during the treatment period through the first 26 weeks, defined as the absence for at least 12 weeks of [1] decrease in platelet count of > 25% from the Platelet Count Pre-PT (Plasma Therapy) Baseline Set-Point; [2] PT while the patient is receiving eculizumab, and [3] new dialysis.
- If the primary study objective was met, then another primary objective was to assess the number of patients who achieved a Haematologic Normalization from baseline (BL) through 26 weeks as well as to the data cut-off date. Haematologic Normalization was defined as normalization of platelet count and LDH sustained for at least two consecutive measurements for at least 4 weeks. This analysis was requested by the regulatory authorities.

The secondary objectives were as follows:

- Evaluate additional efficacy endpoints during the treatment period to the first 26 weeks as well as to the data cut-off date, such as the effect of eculizumab on:

  - TMA Intervention Rate (# PT and # Dialysis Events/Patient/Day) at the end of the first 26 weeks of the Treatment Period compared with the TMA Intervention Rate during the Observation Period to the first eculizumab dose

- Reduction of TMA as indicated by thrombocytopenia and measured by platelet count change from baseline during the first 26 weeks of the treatment period

- Quality of Life measures

- Renal function measures

- Hemoglobin levels

- LDH Response

- Complete TMA Response (analysis requested by the regulatory authorities)

- Characterize the overall safety and tolerability of eculizumab.
- Describe the pharmacokinetics (PK) and pharmacodynamics (PD) properties of eculizumab in patients with aHUS.
- Perform a series of exploratory efficacy analyses on the following by using the available data from the pre-eculizumab treatment and eculizumab treatment periods to quantify differences once patients begin treatment with eculizumab

Statistical Methods and Sample size

The intent-to-treat (ITT) population was used for all efficacy and safety analyses. The ITT population was defined as all patients who received any amount of eculizumab, and were considered evaluable for safety analyses. The first dose of eculizumab in the Treatment Period was considered as study Day 0. The study day was presented and calculated relative to the first dosing day.

The patient's data cut-off date for this study occurred on or before 18 October 2010, which afforded a minimum 26-week Treatment Period for all patients who continued in the study.

The main analysis for this study was based on the pooled data of the two protocols: the protocol for adult patients (C08-003A) and the protocol for adolescent patients (C08-003B).

With a total of 20 patients enrolled between both protocols and, assuming that the true expected probability of TMA Event-Free exacerbation for eculizumab-treated patients is 40%, then the study had approximately 93.5% statistical power to detect a statistically significant difference from a minimum probability (Ho: $P=P_{min}$ v/s Ha: $P>P_{min}$) when $P_{min}=10\%$, 80.8% when $P_{min}=15\%$, and 61.0% when $P_{min}=20\%$. Up to approximately 30 patients were to be enrolled between the protocols of adult and adolescent patients.

Efficacy endpoints

For all efficacy endpoints, the main analyses were based on the pooled data from the two protocols: from protocol C08-003A for adult patients with aHUS and from protocol C08-003B, a similar protocol, for patients <18 years of age for adolescent patients with aHUS

Although this study had two primary endpoints, they were not "co-primary endpoints". If the protocol-specified primary endpoint of TMA Event-Free status from baseline was statistically significant, then an additional efficacy primary endpoint of Hematologic Normalization was also evaluated. Hematologic Normalization was added as a primary efficacy endpoint after discussions with the regulatory authorities while TMA Event-Free status was mandated by the protocol.

- **TMA Event-Free Status**

The point estimate and exact 95% CIs for the proportion of patients attaining a TMA Event-Free status from baseline through 26 weeks were calculated. This proportion (without 95% CIs) was calculated with and without identified complement regulatory factor mutation or auto-antibodies.

The time from Day 0 until the first occurrence of TMA Event-Free status was calculated and the CDF of the time to first occurrence of TMA Event-Free status was generated. The time on the CDF plot represents the target window Data points for individual patients were censored on the CDF plot if the response was sustained as of the date of study discontinuation or early termination.

Of note, TMA Event-Free status was defined as a state in which the patient did not have a PT session, new dialysis, and decrease in platelet count of > 25% from baseline for at least 12 weeks (84 days) and the duration to attain this status is at least 84 days. Therefore, the time that the patient first entered into a TMA Event-Free status is 84 days less than the time when the status is confirmed.

Duration of response is based on the interval in days between the time of occurrence and the last response day or study day (data cut-off date) in which the patient is in TMA Event-Free status. The last response day was the day when the patient no longer met criteria for TMA Event-Free.

- **Haematologic Normalization**

- **Secondary endpoints:**

- TMA Intervention Rate (# PT and # Dialysis Events/Patient/Day) at the end of the first 26 weeks of the Treatment Period compared with the TMA Intervention Rate during the Observation Period to the first eculizumab dose

- Reduction of TMA as indicated by thrombocytopenia and measured by platelet count change from baseline during the first 26 weeks of the treatment period

- Quality of Life measures

- Renal function measures

- Hemoglobin levels

- LDH Response

- Complete TMA Response (analysis requested by the regulatory authorities)

- Characterize the overall safety and tolerability of eculizumab.

- Describe the pharmacokinetics (PK) and pharmacodynamics (PD) properties of eculizumab in patients with aHUS

Results

Participant flow

A total of 23 patients were enrolled in this study. Two patients failed the screening process and one patient withdrew due to personal reasons (Alexion Note to File 02 Feb 2011). Therefore, twenty patients were treated with eculizumab between the protocol for adult patients (C08-003A, 15 adult patients) and the separate protocol for adolescent patients (C08-003B, 5 adolescent patients). All 23 patients were included in the individual data listings. For efficacy and safety analyses, the 20 patients who received at least one dose of eculizumab were included in the intent-to-treat (ITT) population.

Table 22: Patient disposition

Characteristic	N (%)
Enrolled	23 (100)
Treated	20 (87)[a]
Status at data cut-off date	
Off Eculizumab	1 (5)[b]
On Eculizumab	19 (95)[b]
Reason off-eculizumab	
Completed maintenance phase, is not continuing in the extension study	1 (5)[b]

Note: waivers for patient enrollment are discussed in Section 10.2.
a = % of enrolled patients
b = % of treated patients

Conduct of the study

The original protocol for Study C08-003A/B was finalised on 05 Nov 2008 and was subsequently amended four times:

Key changes from the initial Protocol C08-003A/B included:

- Changes in the inclusion/exclusion criteria
- Inclusion of additional efficacy endpoints
- Change from PP analysis to ITT analysis
- Analysis based on the adolescents and the adult protocols alone were not performed
- Changes to the Planned Analyses as Described in the Final SAP

Several patients had normal LDH at the time of screening due to frequent PT administration. The original protocol (Inclusion Criterion 6) required that LDH level be > upper limit of normal (ULN) at screening. Protocol (Version 1) was subsequently amended (Version 2) to allow normal LDH levels at time of screening with requirement that patient had been receiving PE and LDH at the onset of the current aHUS episode was at least ULN or other markers indicative of ongoing hemolysis were present, such as low haptoglobin levels or presence of schistocytes.

Most patients were on immunosuppressant medications and/or Erythrocyte Stimulating Agents (ESAs). Exclusion Criteria 32 and 33 of the protocol required that the dose of immunosuppressant and ESAs remained unchanged in the 4 weeks prior to screening. The changes in dosing were made according to the patients' medical condition. These changes in dosing in the 4 weeks prior to screening did not confound the efficacy endpoints of the study.

Baseline demographics

Table 23: Patient demographic characteristics

Characteristic	Summary Statistics (N=20)
Age at Visit 1 (years) Median (Min; Max)	 28 (13; 63)
Population Age Category [n (%)]	
Adolescent (12 to <18 years)	5 (25)
Adult (≥18 years)	15 (75)
Sex [n (%)]	
Female	12 (60)
Male	8 (40)
Proportion of Patients with any Complement Regulatory Factor Mutation or Auto-Antibody Identified [n (%)]	14 (70)
Proportion of Patients with One Mutation Proportion of Patients with Multiple Mutations	8 (40) 6 (30)
Type of Mutation: Anti-Factor H Antibody - Qualitative	 1 (5)
CD46 (MCP) - Mutation	1 (5)
CD46 (MCP) - Mutation, Factor I - Mutation	1 (5)
CFHR1, CFHR3 – Mutations	1 (5)
CFHR3-CFHR1, CFHR3 – Mutations, Anti-Factor H Antibody - Qualitative	1 (5)
Factor B - Mutation	1 (5)
Factor H – Mutation	3 (15)
Factor H, C3-Mutations	1 (5)
Factor H, CFHR1, CFHR3 – Mutations	1 (5)
Factor I – Mutation	2 (10)
Factor I, C3 - Mutations	1 (5)

Baseline disease characteristics

As shown in Table 24, most patients in this study had a long history of aHUS with a median time from first diagnosis to screening of 48 months. Of the 20 patients treated with eculizumab, 8 patients (40%) had at least one kidney transplant.

Table 24: Summary of patient aHUS disease history

	Summary Statistics
Time from aHUS diagnosis until screening (Months)	
Mean (SD)	87 (87)
Median (Min; Max)	48 (0.66; 286)
Kidney transplant (n[%])	8 (40)
First presentation of aHUS (n[%])	5 (25)

Table 25: Summary of current patient aHUS exacerbation history

Characteristics	Summary Statistics (N=20)
Time from current exacerbation until screening (Months)	
N (patients)	20
Mean (SD)	14 (13)
Median (Min; Max)	8.6 (1.2; 45)
Number of PT sessions during current exacerbation	
Mean (SD)	83 (53)
Median (Min; Max)	62 (20; 230)
Number of PT sessions within 7 days prior to the first dose	
Mean (SD)	1.6 (0.68)
Median (Min; Max)	1.5 (1; 3)
Proportion of patients with dialysis within 56 days of the first dose of eculizumab	2 (10%)

The majority of patients had platelet count ≥ 150 x10^9/L (17/20, 85%) and normal LDH (16/20, 80%) at entry as these parameters were maintained by the ongoing chronic PT. As might be expected as a consequence of chronic PT, all patients had various degrees of renal insufficiency and 10 patients (50%) had either severe or very severe renal insufficiency (CKD Stage 4 and 5), including 2 patients on chronic dialysis.

Table 26: Baseline characteristics of clinical laboratory values

Characteristic	Summary Statistics (N = 20)
Platelet Count ($x10^9$/L)	
Mean (SD)	228 (78)
Median (Min; Max)	218 (105; 421)
Number of patients (% of Total) in respective platelet category [n (%)]	
< 150 $x10^9$/L	3 (15)
≥ 150 $x10^9$/L	17 (85)
LDH (U/L)	
Mean (SD)	223 (70)
Median (Min; Max)	200 (151; 391)
Number of patients (% of Total) in respective LDH Category [(n %)]	
≤ ULN	16 (80)
> ULN	4 (20)
Creatinine (µmol/L)	
Mean (SD)	287 (215)
Median (Min; Max)	234 (106; 893)
Number of patients [n (%)] with eGFR (mL/min/1.73*m^2) categorized as follows	
<15	4 (20)
15-29	6 (30)
30-44	6 (30)
45-59	2 (10)
60-89	2 (10)
≥90	0 (0)
Number of patients [n (%)] within each CKD Stage	
Stage 1	0 (0)
Stage 2	2 (10)
Stage 3a	2 (10)
Stage 3b	6 (30)
Stage 4	6 (30)
Stage 5	4 (20)

Primary endpoint:

1. TMA Event-Free Status

A substantial majority of patients receiving eculizumab in the study (16 of 20 patients [80%; 95% CI: 56- 94]) achieved the primary endpoint of TMA Event-Free Status through Week 26, which was sustained for a median time duration of approximately 40 weeks (280 days) as of the data cut-off date. The median time to attain a confirmed TMA Event-Free status was 12 weeks (84 days).

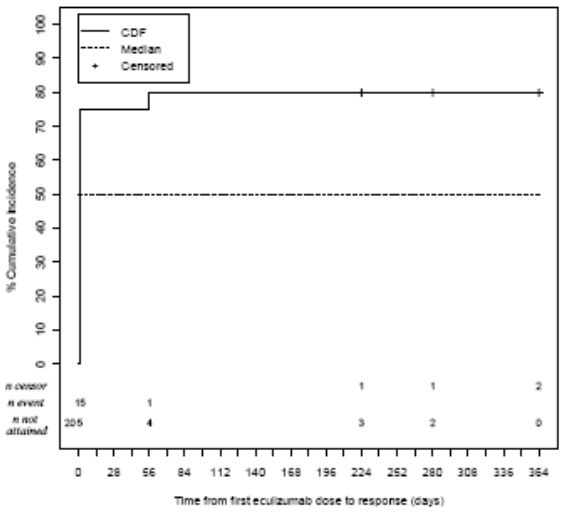
Table 27: Summary of TMA event-free status through 26 weeks

	Number of Patients with Improvement/Total patients (%)	Maximum Duration (Days)	
		n	Median (Min;Max)
All patients (N=20)	16/20 (80)	16	181 (126; 183)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=14)	12/14 (86)	12	181 (126; 182)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=6)	4/6 (67)	4	182 (181; 183)

The four patients who did not achieve TMA event-free status had normal platelet count at study entry and maintained these levels (≥ 150 x 10^9/L) during the Treatment Period. However, at certain time points, these patients had changes in their platelet count that exceeded the strict criteria of less than 25% change from baseline required for achieving a TMA event-free status.

The cumulative incidence, i.e., the Cumulative Density Function (CDF), of the TMA Event-Free status was also estimated and plotted and shown in Figure 1 below. Duration of response is based on the interval in days between the time of occurrence and the last response day or study day (data cut-off date) in which the patient is in TMA event-free status. As of the data cut-off date, the duration of response in patients ranged from 126 to 364 days

Time to First Occurrence
(All Patients, N=20)



Duration
(Responders, n=16)

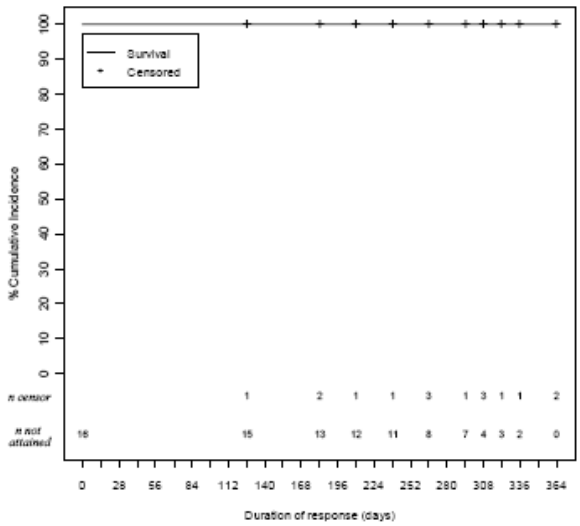


Figure 8: TMA event-free status - Time to first occurrence and duration

2. Hematologic Normalisation

Haematologic normalisation was achieved in almost all patients, demonstrating maintenance of normal platelet count after discontinuation of PT and start of eculizumab therapy. As shown in Table 28 below, a total of 18 out of 20 patients (90%; 95% CI: 68-99) achieved Hematologic Normalization, including 1 of the 3 patients who had baseline platelet count <150 x 10^9/L. Similar proportion of patients achieved Hematologic Normalisation with or without identified complement regulatory factor mutation or auto-antibody.

Table 28: Haematologic normalisation from baseline through data cut-off date

	Number of Patients with Improvement/Total patients (%)	Maximum Duration (Days)	
		n	Median (Min; Max)
All patients (N=20)	18/20 (90)	18	267 (154; 363)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=14)	13/14 (93)	13	294 (181; 336)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=6)	5/6 (83)	5	203 (154; 363)

Platelet count and LDH responses to eculizumab, as of the data cut-off date, are summarised as follows:

- For the 2 of the 3 patients with abnormal platelet count at baseline, platelet count normalization was achieved in 1 and 7 days following the first eculizumab dose (Figure 10). Only one of these 2 patients achieved the platelet count normalization state required for Hematologic Normalization and maintained it for 301 days.

- For the 4 patients with abnormal LDH at baseline, the time to first occurrence of LDH normalization occurred between 3 and 14 days following the first eculizumab dose, with a median time of 7 days to achieve the first occurrence of LDH normalization (Figure 11). LDH normalization was sustained from 28 to 48 weeks (196 to 336 days) after the first eculizumab dose (Figure 11).

The median time to the first occurrence of Hematologic Normalisation was 1 day (Figure 9). Maximum length of Hematologic Normalisation was sustained for a median duration of approximately 38 weeks (267 days) and ranged from 22 to 52 weeks (154 to 363 days). All patients who achieved Hematologic Normalisation while on eculizumab continued to show normal platelet count or normal LDH levels at the date of the last record (as of the data cut-off date) (Figure 9).

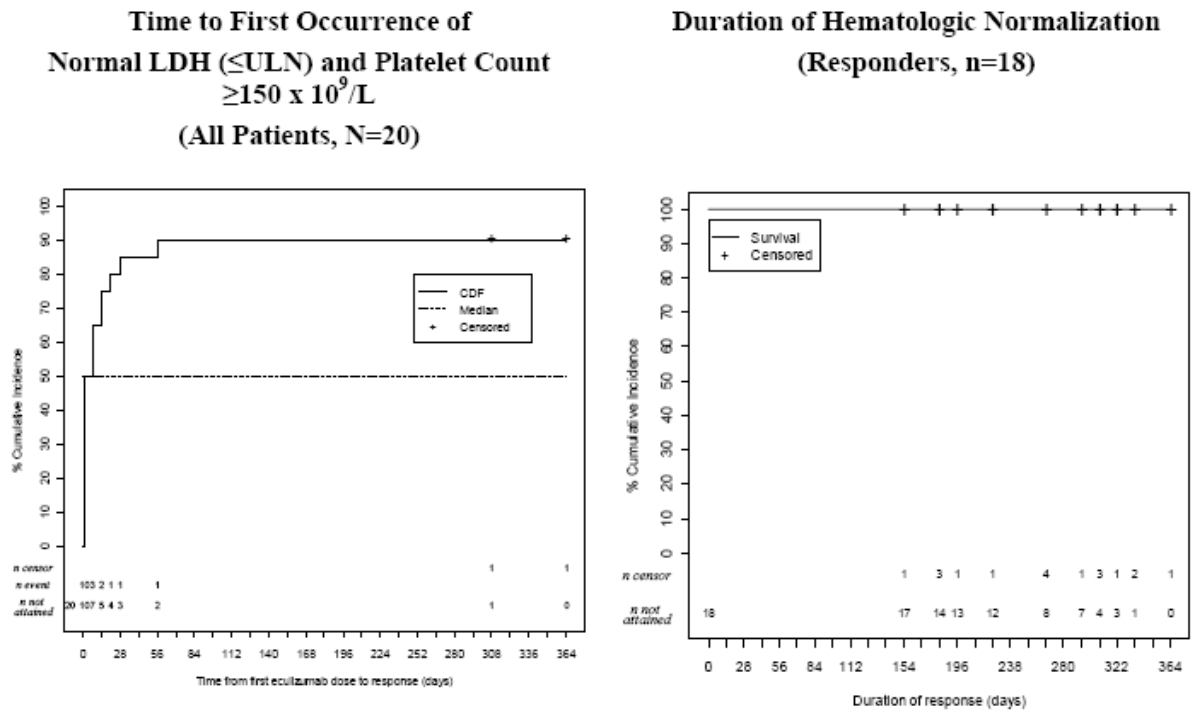


Figure 9: Haematologic normalisation - Time to first occurrence and duration

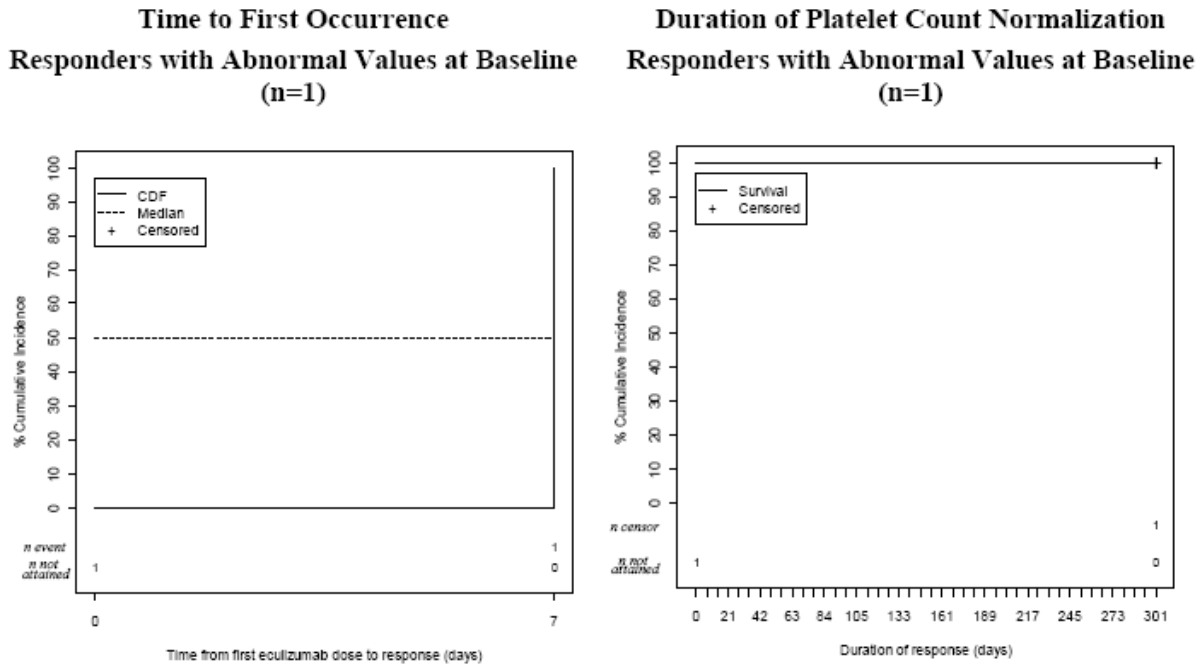


Figure 10: Platelet count normalisation (≥ 150 x 10^9/L) – Time to first occurrence and duration

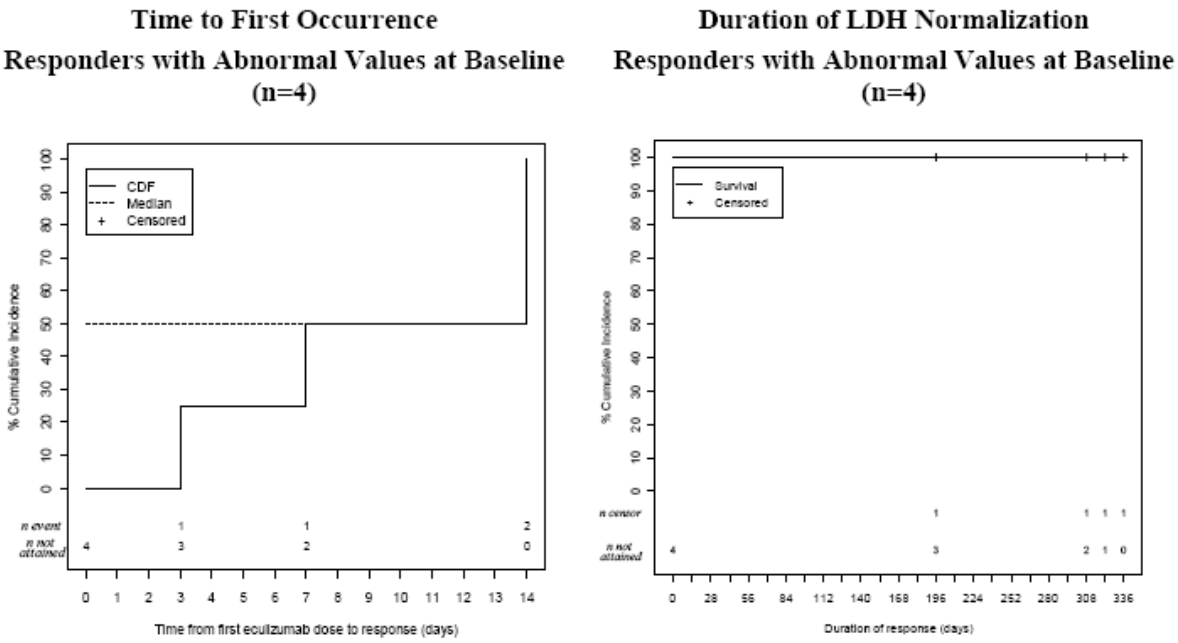


Figure 11: Normal LDH (≤ULN) - Time to first occurrence and duration

Key Secondary endpoints

TMA Intervention Rate

The TMA Intervention Rate was reduced from a median of 0.23 events/person/day to 0 events/person/day (Table 29). The difference in the TMA intervention rates prior to eculizumab treatment versus the eculizumab treatment period, as assessed using the signed rank test, was statistically significant (P <0.0001).

Table 29: TMA intervention rates pre-eculizumab treatment and during eculizumab treatment from baseline through data cut-off date

Intervention Rate	Pre-Eculizumab Treatment [a] (N=20)	During Eculizumab Treatment [b] (N=20)	*P*-value (Signed-Rank)
Intervention rate per patient (PT sessions and dialysis/patient/day) Median (Min; Max)	0.23 (0.05; 1.09)	0	< 0.0001
Number of patients (% of Total) with a dialysis event (pre-eculizumab treatment) or new dialysis[c] (during eculizumab treatment)	2 (10.0%)	0 (0.0%)	N/A
Number of patients (% of Total) receiving Plasma Therapy	20 (100%)	0 (0%)	N/A
Number of Plasma therapies per patient Median (Min; Max)	10 (3; 25)	0	N/A

[a] From the start of the Observation Period to the first eculizumab dose
[b] From first eculizumab dose to (1) 26 weeks after the first eculizumab dose and (2) the data cut-off date
[c] Only dialysis occurring on or after 15 days following the first dose are counted in the during treatment period
N/A = Not applicable

Complete TMA Response

Complete TMA Response (analysis requested by the regulatory authorities.), was defined as Hematologic Normalisation plus improvement in renal function (25% reduction from baseline in serum creatinine, which was sustained for two consecutive measurements which span a period of at least four weeks)

Complete TMA Response was observed in 5 out of 20 patients (25%; 95% CI: 9-49) (Table 30). One (out of five patients treated for their first presentation of aHUS achieved a Complete TMA Response. This might be expected considering the chronic status of these patients and, particularly of the renal impairment. The question remains on how many patients decreased renal function while on eculizumab treatment. Complete TMA Response rates were similar in patients with or without identified complement regulatory factor mutations or auto-antibodies

Table 30: Complete TMA response

	Number of Patients with Improvement/Total patients (%)	Maximum Duration (Days)	
		n	Median (Min; Max)
All patients (N=20)	5/20 (25)	5	224 (83; 266)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=14)	3/14 (21)	3	224 (140; 238)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=6)	2/6 (33)	2	175 (83; 266)

Source: Table 14.3.7a
Note: Patient had a kidney transplant on Day 217 and, therefore, this patient's data after Day 217 was excluded in this analysis.

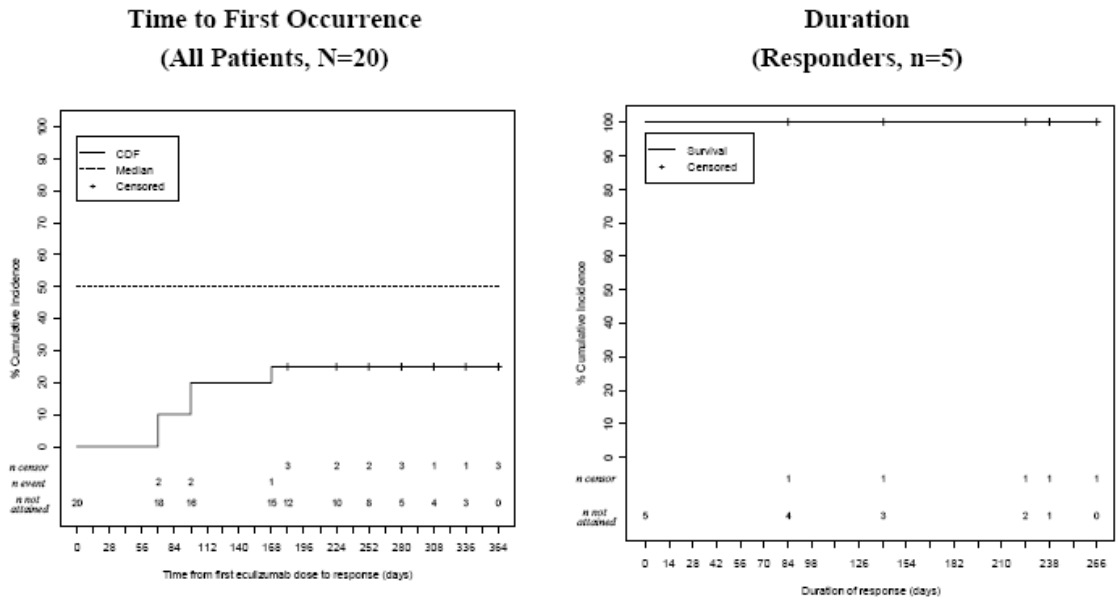


Figure 12: Complete TMA response - Time to first occurrence and duration

Platelet Count Change From Baseline

The ANOVA of change from baseline platelet count at each on-treatment day of measurement through 26 weeks (Day 182) demonstrated a statistically significant (P<0.05) increase on Days 14 and 21 after the start of eculizumab treatment

Table 31: Statistical assessment of change from baseline platelet counts

Study Day	N	**Point Estimate**	**95% CI**	***P*-value**
Day 14	20	32.18	9.44; 54.92	0.0066
Day 21	20	32.08	9.34; 54.82	0.0067
Week 26 (Day 182)	20	5.28	-17.46; 28.02	0.6424

Platelet count normalization (≥150 x 10^9/L) was achieved in 18 out of 20 (90%) patients. Patients with normal platelet count at baseline maintained that level after PT was discontinued and the switch to eculizumab treatment initiated. Platelet count remained stable with a minimal mean increase of 5.3 × 10^9 cells/L by Week 26.

Change in Renal Function Parameters

Table 32: Proportion of patients with improvement in renal function from baseline through data cut-off date

	Number of Patients with Improvement/Total patients (%)	
	At Least One Measurement Demonstrating Improvement	**Sustained**
eGFR improvement ≥15mL/min/1.73 m^2		
All patients, (N=20)	4/20 (20)	2/20 (10)
Positive for Complement Regulatory Factor Mutation or Auto-antibody, (n=14)	3/14 (21)	1/14 (7)
No Identified Complement Regulatory Factor Mutation or Auto-antibody, (n=6)	1/6 (17)	1/6 (17)
Improvement in CKD Stage		
All patients, (N=20)	9/20 (45)	7/20 (35)
Positive for Complement Regulatory Factor Mutation or Auto-antibody, (n=14)	5/14 (36)	4/14 (29)
No Identified Complement Regulatory Factor Mutation or Auto-antibody, (n=6)	4/6 (67)	3/6 (50)
Creatinine decrease of at least 25% from baseline		
All patients, (N=20)	8/20 (40)	4/20 (20)
Positive for Complement Regulatory Factor Mutation or Auto-antibody, (n=14)	6/14 (43)	3/14 (21)
No Identified Complement Regulatory Factor Mutation or Auto-antibody, (n=6)	2/6 (33)	1/6 (17)

Source: Table 14.3.4.4a
CKD: Including Stages 1, 2, 3a, 3b, 4 and 5
Note: Patient had a kidney transplant on Day 217 and, therefore, renal count improvements after this day were excluded from this analysis.

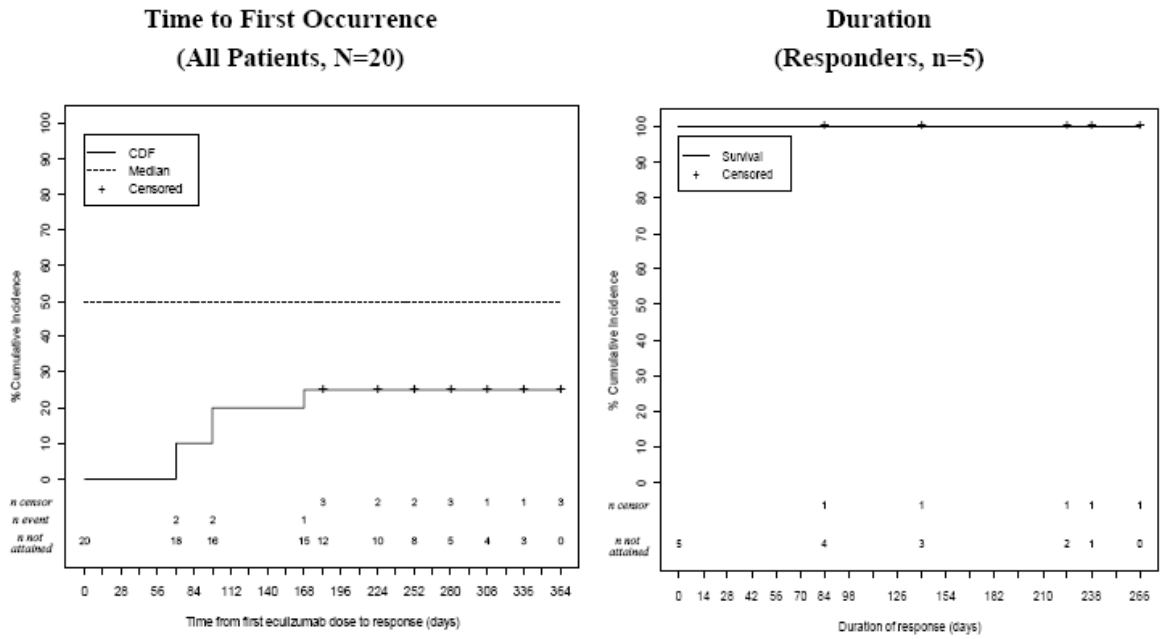


Figure 13: Decrease of creatinine ⩾25% from baseline - Time to first occurrence and duration

Change in Haemoglobin

Table 33: Proportion of patients with improvement in haemoglobin through data cut-off date

	Number of Patients with Improvement/Total patients (%)	
	At Least One Measure Demonstrating Improvement	Sustained[a]
Hemoglobin improvement ≥20 g/L		
All patients, (N=20)	10/20 (50)	10/20 (50)
Positive for Complement Regulatory Factor Mutation or Auto-antibody, (n=14)	7/14 (50)	7/14 (50)
No Identified Complement Regulatory Factor Mutation or Auto-antibody, (n=6)	3/6 (50)	3/6 (50)

[a]Sustained is defined as two consecutive visits spanning at least four weeks

Quality of life

Results from the EuroQol 5D Quality of Life instrument comparing scores between baseline and 26 weeks indicated statistically significant (P <0.0001) improvements in QoL with eculizumab. Improvements were also statistically significant (P<0.05) in the EuroQol 5D scores from baseline through the data cut-off date. Furthermore, a substantial proportion of evaluable patients, 8 out of 11 patients (73%) achieved a minimally important difference (MID) of 0.06 in the EuroQol 5D to the data cut-off date and Week 26.

Other secondary endpoints

From baseline to the data cut-off date, 10 of 20 patients (50%; 95% CI: 27−73) experienced an improvement in hemoglobin of at least 20 g/L and a large majority of patients, 19 of 20 patients (95%, 95% CI: 75-100), experienced decreased LDH levels below the ULN during the eculizumab treatment period.

Prior to the start of eculizumab treatment (pre-treatment or Observation Period), all 20 patients required PT and all 20 patients (100%) did not require PT during eculizumab treatment through to the data cut-off date (at least 26 weeks). The comparison of the PT rates from the signed-rank test showed a statistically significant (P-value= <0.0001) decrease in the PT rates during eculizumab treatment

Subgroups analyses

There were no apparent differences in any of the endpoints between patients with complement regulatory factor mutations or auto-antibodies compared with those with no identified complement regulatory factor mutations or auto-antibodies. There was no examination of efficacy or safety by demographic (e.g., race, age) characteristics for this study report

Updated results from studies C08-002A/B and C08-003A/B

To further support the sustained efficacy and demonstrate the long-term benefit of eculizumab treatment in aHUS patients, Alexion conducted an updated analysis of the prospective trials with approximately 6 months of additional follow-up. All patients from studies C08-002A/B and C08-003A/B who were on treatment at the time of the submission data cut-off remained on treatment at the time of this follow up analysis (Table 1). All efficacy data were collected until March 15, 2011. The median follow-up was 64 weeks in study C08-002A/B and 62 weeks in study C08-003A/B. A total of 5 patients (4 in study C08-002A/B) and 1 in study C08-003A/B) had discontinued eculizumab therapy at the time of the initial submission and none discontinued therapy during the extended follow-up period. In study C08-002A/B, 13/13 patients who remained on therapy have a follow-up period of at least 52 weeks. In study C08-003A/B, the corresponding number was 15/19 patients.

Table 1: Duration of Therapy in Prospective Studies C08-002A/B and C08-003A/B

Parameter	C08-002A/B N= 17		C08-003A/B N= 20		Total N= 37	
	Submission	Update	Submission	Update	Submission	Update
Mean (SD), weeks	38 (19.34)	58 (28.58)	39 (9.33)	60 (11.96)	39 (14.59)	59 (20.96)
Median, weeks	38	64	40	62	38	64
Range, weeks	2 - 64	2 - 90	26 - 52	26 - 74	2 - 64	2 - 90
<12 weeks, n (%)	2 (12)	2 (12)	0	0	2 (5)	2 (5)
12-<26 weeks, n (%)	0	0	0	0	0	0
26-<52 weeks, n (%)	10 (59)	2 (12)	18 (90)	5 (25)	28 (76)	7 (19)
≥52 weeks, n (%)	5 (29)	13 (76)	2 (10)	15 (75)	7 (19)	28 (76)

Study C08-002A/B

With longer follow-up, a sustained improvement in some of the clinical response parameters was observed including platelet count normalization, haematologic normalization, complete TMA response, decrease in creatinine ≥25%, CKD improvement and haemoglobin improvement (Table 2). These efficacy measures illustrate that although responses usually occur rapidly as demonstrated in the

original submission, some patients required longer duration of treatment before achieving key improvements in haematologic and renal function despite early control of the TMA process.

Table 2: Primary Endpoints in Study C08-002A/B

	No (%) of patients		
	26 weeks	**Submission cut-off**	**Update**
Platelet count > 150 x10^9/L	14	14	15 (88)
Hematologic normalization	13 (76)	13	15 (88)
Complete TMA response	11 (65)	11	13 (76)
TMA event-free	15 (88)	15 (88)	15 (88)
Decrease in creatinine ≥25%	11 (65)	11 (65)	13 (76)
Increase in eGFR ≥15 mL/min/1.73m^2	8	9 (53)	9 (53)
CKD improvement ≥ 1 stage	10	10	11 (65)
Hemoglobin improvement ≥20 g/L	11 (65)	12	13 (76)

The duration of response to eculizumab treatment has been remarkable. At the time of this update, all patients maintained their response with the exception of one patient who lost TMA event-free status due to 5 plasma therapy sessions after 9 months of eculizumab therapy. All patients who achieved platelet normalisation, improvement in renal function, haematologic normalisation and complete TMA response maintained that response at the time of the last follow-up.

Study C08-003A/B

With the additional follow-up period, there was evidence that patients who were on chronic eculizumab continue to derive important clinical benefit over time (Table 3). Overall, we observed an increase in the rate of complete TMA response as well as a significant improvement in renal function in some patients over this extended treatment duration (Figs. 6 and 7).

Table 3: Key Endpoints in Study C08-003A/B

	No (%) of patients		
	26 weeks	**Submission cut-off**	**Update**
Hematologic normalization	18	18	18
Complete TMA response	5	5	7
TMA event-free	16	16	17
Decrease in creatinine ≥25%	3	4	7
Increase in eGFR ≥15 mL/min/1.73m^2	1	2	3
CKD improvement ≥ 1 stage	7	7	9

Fig 6: Duration of TMA event-free status

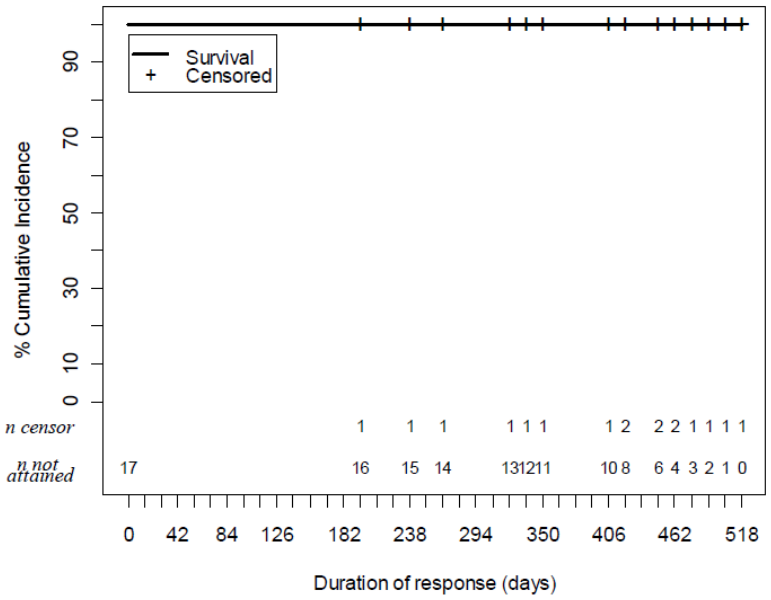
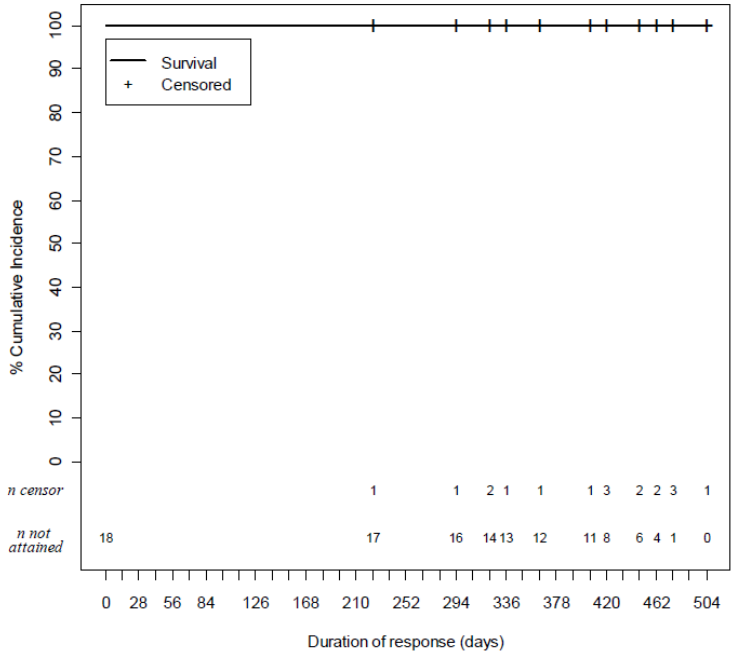


Fig 7: Duration of Hematologic Normalization



3.3.3.3. Clinical studies in special populations

Study C09-001r

Design

This was a retrospective data collection trial consisting of male or female patients with a diagnosis of aHUS and who fulfilled the predefined parameters (had received at least one dose of eculizumab

outside of an Alexion-sponsored controlled clinical trial between 2007 and Dec 2009). These patients had never participated in, nor were concurrently participating in a controlled trial of eculizumab. Alexion contacted the physicians of the pre-identified patients to discuss the nature, design and objectives of the study trial and their willingness to participate in the retrospective trial. Subsequently, the pre-identified patients (or legal guardian, if patient was a minor) were contacted by their treating physician and provided an ICF or IA.

This retrospective study consists of 30 patients (paediatric, adolescent and adults) who had been treated with eculizumab for de novo or recurrent aHUS outside of an Alexion-sponsored controlled clinical trial. The C09-001r is a retrospective study with no control groups. In several statistical analyses, each patient's historical experiences (if available) and data collected prior to the first dose of eculizumab treatment were used as comparators to the data collected during eculizumab treatment.

Study Participants

Inclusion/exclusion criteria included:

1. Male or female patients of any age who had been diagnosed with aHUS.
2. Received at least one dose of eculizumab for the treatment of aHUS between 2007 and 2009 outside of an Alexion-sponsored clinical trial.
3. Patients who had participated or who were concurrently participating in a controlled clinical trial of eculizumab. (exclusion criterium)

Treatments

This is a retrospective data collection study and therefore no treatments were prescribed. The treatment period described below refers to the physicians' use of commercial Soliris and structure of the data collection.

This study was divided into four periods of retrospective observation (Initial Pre-Treatment, 30 Day-Pre-Treatment, Treatment and the Post Treatment Period whenever data was available). The type of treatment received for aHUS prior to the treatment period may have included plasma therapy, immunosuppressant therapy, kidney transplant, nephrectomy, dialysis, and/or supportive care. The Treatment Period commenced with the first eculizumab dose administered intravenously. The total duration of the eculizumab treatment varied for each patient, ranging from a single dose to chronic therapy.

The treatment or the time of the last eculizumab dose or the signing of ICF/IAF for this trial (if the patient is continuing on drug at the signing of the ICF/IAF) defined the time period for assessments of the study endpoints attributed to eculizumab.

For patients in this study, the eculizumab regimen administered was determined at the discretion of the Investigator/treating physician. Physicians treating patients in the off-label setting generally requested dosing suggestions from Alexion. The dosing regimen recommended for all adolescent and adult patients weighing at least 40 kg was that specified in the prospective aHUS clinical studies (C08-002A/B and C08-003A/B). The dosing regimen recommended for pediatric and adolescent patients weighing less than 40 kg was defined based on body weight. The dose levels of eculizumab administered to patients by the physicians were provided by Alexion and based on recommendations according to PK-PD modeling. The actual dose administered to some patients in this retrospective study may have been different from the recommendations since treatment was outside of a controlled clinical trial setting. Dose levels used on this study were 300 mg, 600 mg, 900 mg and 1200 mg.

Objectives

The objective of this retrospective trial was to assess the safety and efficacy of eculizumab in aHUS patients treated with at least one dose of eculizumab outside of an Alexion-sponsored controlled clinical trial.

Statistical Methods and Sample size

Descriptive statistics of efficacy parameters were presented for 30 Day-Pre-Treatment and during the Treatment period (whenever data were available). Changes in parameters occurring during treatment were compared to the baseline value.

The platelet count change from baseline was evaluated by a model which used target day as a classification variable. Time and baseline (BL) were the main effects. Patient entered the model as a random effect. Repeated measurements made in time within each patient were modelled using an appropriate variance-covariance matrix structure.

The difference in the pre- and during treatment TMA intervention rates was calculated for each patient using a five-step algorithm. The P-value for this test came from a two-sided signed rank test.

Renal function parameters, creatinine and eGFR, were assessed by frequency counts, proportions, and exact 95% CI's for obtained pre-treatment and during treatment and change from baseline to the end of study were produced. Shifts in CKD stage by Target Day were generated to determine whether renal function improved or worsened. Additional analyses on patients whose eGFR improved by at least 15 mL/min/(1.73 m^2) from baseline, whose creatinine decreased at least 25% from BL through and who improved at least one stage in CKD from baseline through 26 weeks and until the date of the last record were produced. Analyses for renal function was performed for all patients as well as for subgroups defined by presence or absence of complement factor mutations. Exact 95% CI's were produced only in the analysis where all patients were grouped together.

Frequency counts, proportions, and exact 95% CI's for patients whose hemoglobin improved by at least 20 g/L and whose LDH was below the respective ULN from baseline through 26 weeks and at until the date of the last record were produced and categorized by with or without identified complement mutation.

Efficacy endpoints and endpoints requested by the regulatory authorities (Haematologic Normalisation and Complete TMA Response) were based largely on analyses that were planned for the prospective studies C08-002A/B and C08-003A/B.

For inferential statistics of efficacy, the Last Observation Carried Forward (LOCF) method of imputation of missing values was performed for platelet count until Week 26. For patients with missing values observed after at least one post-baseline measurement, the last post- baseline assessment observed prior to the particular missing observation was used as the LOCF value for that observation. For patients where only a baseline value existed, no LOCF imputation was performed.

In this retrospective study, patients were assessed for change in platelet count from baseline, platelet count normalization, the TMA Event-Free status and the TMA intervention rates including the proportion of patients who successfully discontinued PT. Additional endpoints were also assessed. Given the nature of a retrospective data collection, extent of dosing, frequency of laboratory testing and tests performed were variable. Some of the pre-specified analyses (also used in the two prospective studies), in particular the composite endpoints of Hematologic Normalization and Complete

TMA Response, had important analytical limitations. Due to these limitations, a sponsor assessment was performed using criteria similar to those which were applied in the prospective studies.

The available PK and PD results for some patients where PK/PD tests were requested by their treating physicians were tabulated. A population PK/PD analysis of eculizumab was performed using data from adult and adolescent patients with plasma therapy-resistant aHUS (C08-002A/B) and plasma therapy sensitive aHUS (C08-003A/B) patients, and data from paediatric, adolescent and adult patients collected on a retrospective basis (C09-001r).

Efficacy endpoints

• Platelet count
The platelet count change from baseline will be evaluated using two different classes of models which are differentiated by the use of study day as either a classification variable or as a continuous variable.
• Difference in TMA intervention rates pre- and postdose
TMA intervention rate is defined as the number of Plasma Therapy or Dialysis Events per day per patient. The TMA Intervention Rate during the Treatment Period will be compared with the TMA Intervention Rate in the one month (four weeks) prior to the first dose of eculizumab.
• TMA event-free status
TMA Event-Free status is defined as the absence for at least 12 weeks of [1] decrease in platelet count of >25% from the baseline platelet count; [2] PT while the patient is receiving eculizumab, and; [3] new dialysis while the patient is receiving eculizumab. The time to start of first TMA Event-Free state and the average maximum duration of TMA Event-Free status will be calculated.
• Hemoglobin
Frequency counts, proportions, and exact 95% CI's for patients whose hemoglobin improved by at least 20 g/L at the end of study involvement will be produced.
• Lactate dehydrogenase (LDH) Frequency counts, proportions, and exact 95% CI's for patients whose LDH was below the respective Upper Limit of Normal will be produced.
• Parameters associated with renal function
Frequency counts, proportions, and exact 95% CI's for patients who improved at least one CKD stage from BL to the end of study will be produced. Additional analyses on patients whose eGFR improved by at least 15 mL/min/(1.73 m^2), and whose creatinine decreased at
least 25% will be produced.
• Parameters associated with intravascular hemolysis
Markers of intravascular hemolysis include assessments such as haptoglobin levels and presence of schistocytes. Any of these measurements which exist in the data will be listed.
• Pharmacokinetic (PK) and Pharmacodynamic (PD) measures as available
Since PK and PD tests were performed on some patients at the requests of their treating physicians the available PK and PD results from those patients will be listed and summarized.
• Major adverse vascular event (MAVE) rate
All MAVE events that occur pre-treatment and during treatment periods will be listed and tabulated. Any MAVE events that occurred prior to this study and are recorded in the data base will be listed and tabulated.

Following the analyses in the prospective studies, two post-hoc efficacy endpoints have been added to this study. Assessing these post-hoc efficacy endpoints involve determining if certain lab parameters are in normalized states. Time in the Post-Treatment period will be included in the calculation of duration of these states.

• Hematological Normalization

Hematological Normalization requires normalization of both platelet count and LDH.

• Complete TMA Response

Complete TMA Response is defined as hematological normalization plus improvement in renal function

Results

Participant flow

Alexion was able to identify 36 patients who were diagnosed with aHUS and treated with eculizumab between 2007 and Dec 2009 outside the two Alexion-sponsored controlled clinical trials. Data were compiled retrospectively for aHUS patients undergoing treatment with eculizumab in an uncontrolled clinical setting.

Of the 36 patients identified, 30 patients agreed to participate. The remaining six patients were not included in the trial for the following reasons: two patients declined participation and the treating physicians for four other patients declined participation in this retrospective trial. Data from 30 patients were collected and presented in this report. The disposition of the 30 patients whose data has been collected is presented below in Table 34.

Four of the 30 patients were not evaluable to assess the efficacy of eculizumab to control TMA associated with aHUS. One adult patient had a TMA episode following bone marrow transplant, and another adult patient had stable disease and did not require PT intervention prior to eculizumab treatment. The remaining two patients were without evidence of clinical manifestations of aHUS disease.

Table 34: Patient disposition

	Number of Patients N= 30
Enrolled	**30 (100%)**
Treated	**30 (100%)**
Treatment Interruption	
No	27 (90%)
Yes	3 (10%)
Reason for Treatment Interruption	
Other: Physician's decision	1 (3%)
Patient condition improvement	2 (7%)
Treatment Discontinuation	
No	19 (63%)
Yes	11 (37%)
Reason for Treatment Discontinuation	
Administrative decision	1 (3%)
Death[a]	2 (7%)
Lack of efficacy	6 (20%)
Other: Normalization of hematologic and renal function parameters	1 (3%)
Patient / parents requested to withdraw	1 (3%)

%= percentage of total number of patients

[a]Patient died of carotid artery dissection and stroke; Patient died due to pulmonary aspergillosis and worsening graft versus host disease; both deaths were unrelated to Eculizumab.

Baseline demographics

Table 35: Patient demographic characteristics

Characteristic	Summary Statistics (N=30)
Age at First Dose (years)	
Median (Min; Max)	12 (0.17; 51.4)
Population Age Category [n(%)]	
Infant (<2 years)	5 (17)
Children (≥2 to <12 years)	10 (33)
Adolescent (≥12 to <18 years)	4 (13)
Adult (≥18 years)	11 (37)
Sex [n(%)]	
Female	16 (53)
Male	14 (47)
Proportion of Patients with Any Complement Regulatory Factor Mutation or Auto-Antibody Identified [n(%)]	14 (47)
Proportion of Patients with One Mutation	13 (43)
Proportion of Patients with Multiple Mutations	1 (3)
Type of Mutation [n(%)]:	
Complement Protein 3 (C3) Gain-of-Function Mutation	3 (10)
Membrane Cofactor Protein (MCP) – Mutation	1 (3)
Factor H- Mutation	9 (30)
Factor H- Mutation, Factor I- Mutation, Membrane Cofactor Protein (MCP), Factor B Gain-of-Function Mutation	1 (3)

Source: Table 14.1.2

Demographic and baseline characteristics are summarized in Tables 14.1.2 and 14.1.2a. Individual demographics and baseline characteristics are presented in Listing 16.2.4.1a. A complete list of complement regulatory factor mutation or auto-antibody by patient is presented in Listing 16.2.4.1b.

Baseline disease characteristics

Patients were diagnosed with aHUS for a median (Min; Max) of 10.9 (0.23; 175.90) months prior to the first eculizumab dose. Fourteen of 30 patients (47%) in this retrospective study had at least 2 aHUS exacerbations since initial diagnosis including kidney transplant in 11 patients (37%). Twelve patients (40%) were experiencing their first aHUS presentation. Patients were experiencing the current aHUS exacerbation for a median (min; max) of 1.28 (0.07; 15.77) months prior to the first dose of eculizumab.

Twenty-eight of the 30 patients had a disease history consistent with PT-resistant and chronic PT populations. The remaining two patients exhibited no clinical manifestations of aHUS; one patient was treated with eculizumab following kidney transplant and the other patient was being prepared for kidney transplant but died of complications of vascular surgery of the carotid artery. Twenty patients enrolled in this study with aHUS were assessed by the Sponsor to be PT resistant (similar to the prospective study C08-002A/B) based on a current duration of aHUS exacerbation of ≤2 months. Eight patients enrolled in this study with aHUS were assessed by the Sponsor to be chronic PT (PT-sensitive) patients (similar to the prospective study C08-003A/B) based on a current duration of aHUS exacerbation of >2 months.

Patient aHUS disease history is summarised in Table 36.

Table 36: Summary of patient aHUS disease history

Characteristic	Summary Statistics (N=30)
Number of aHUS exacerbations per patient including the first diagnosis	
N (Patients)	30
Mean (SD)	3.5 (3.27)
Median (Min; Max)	2 (1; 14)
Time from aHUS diagnosis until first dose (Months)	
N (Patients)	30
Mean (SD)	42.27 (56.02)
Median (Min; Max)	10.9 (0.23; 175.90)
Time from Current Exacerbation until first dose (Months)[a]	
N (Patients)	29
Mean (SD)	2.33 (3.01)
Median (Min; Max)	1.28 (0.07; 15.77)
Proportion of patients with prior kidney transplant [n(%)][a]	11 (37)
First presentation of aHUS [n(%)]	12 (40)
Proportion of patients with current duration of aHUS exacerbation ≤2 months (PT-resistant-like, C08-002A/B [n(%)])	20 (67)
Proportion of patients with current duration of aHUS exacerbation >2 months (PT-sensitive-like, C08-003A/B [n(%)])	8 (26)
Proportion of patients without clinical manifestation of aHUS disease [n(%)][b]	2 (7)

[b] Patient had no current aHUS episode; Patient was treated prophylactically post-kidney transplantation (not evaluable)
Source: [a] Table 14.1.2, Table 14.1.4, Table 14.4 (Tabulation of Key Clinical Laboratory Parameters and Individual Patient Summaries) and Listing 16.2.4.3a

Eleven patients (37%) required dialysis for renal failure prior to receiving eculizumab. The majority of patients (24 of 30 patients) received at least one PT session within 28 days prior to the first dose of eculizumab. An average of eight PT sessions was recorded per patient prior to the administration of eculizumab.

Patient current aHUS exacerbation/presentation history is summarised in Table 37.

Table 37: Summary of patient current aHUS exacerbation/presentation history

Characteristic Prior to the First Dose of Eculizumab[a]	Summary Statistic (N=30)
Proportion of patients with at least one dialysis session [n(%)][b]	11 (37)
Proportion of patients with at least one PT session [n(%)][c]	24 (80)
Number of PT sessions per patient	
N (Patients)	30
Mean (SD)	8 (6.90)
Median (Min; Max)	8 (0; 29)

[a] History period is from the later of the start of the current aHUS episode or 28 days prior to first dose.
[b] Patient excluded due to this patient receiving dialysis before current aHUS exacerbation.

Thirteen of 30 patients (43%) had low platelet count (<150x10^9/L) at baseline, and 20 of 30 patients (67%) had an LDH level above the ULN at baseline.

Overall nine patients had both abnormal platelet count and LDH level at entry, which included six of 12 patients (50%) experiencing their first aHUS presentation. A total of 24 patients (80%) had an eGFR less than 60 mL/min/1.73 m^2. The eGFR was consistent with Stage 4 or Stage 5 chronic kidney disease (CKD) in 13 patients. Baseline laboratory values for the patients in this retrospective trial are summarised in Table 38.

Table 38: Baseline characteristics – number of patients

Characteristic	Summary Statistics
Platelet Count ($\times 10^9$/L)	
N (patients)	30
Mean (SD)	171.2 (82.9)
Median (Min; Max)	159 (25; 381)
Number of patients [n(%)] in respective platelet Category	
<150 $\times 10^9$/L	13 (43)
≥150 $\times 10^9$/L	17 (57)
LDH (U/L)	
N (patients)	28
Mean (SD)	602.4 (448)
Median (Min; Max)	453 (158; 1859)
Number of patients [n(%)] in respective LDH Category	
≤ULN	8 (27)
>ULN	20 (67)
Creatinine (µmol/L)	
N	30
Mean (SD)	271.1 (277.7)
Median (Min; Max)	159 (15; 968)
Number of patients [n(%)] with eGFR (mL/min/1.73 m^2) categorized as follows	
<15	8 (27)
15-29	5 (17)
30-44	8 (27)
45-59	3 (10)
60-89	2 (7)
≥90	4 (13)
Number of patients [n(%)] within each CKD stage	
Stage 0 Stage 1	0 (0) 4 (13)
Stage 2	2 (7)
Stage 3a	3 (10)
Stage 3b	8 (27)
Stage 4	5 (17)
Stage 5	8 (27)

Efficacy endpoints:

1. **Platelet Count Change From Baseline and Platelet Count Normalization**

The mean change from baseline platelet count at each on-treatment target day of measurement demonstrated a statistically significant increase in platelet count as early as 14 days (P=0.0007) and up to 364 days (52 weeks) after the first eculizumab dose. By Week 52, the mean increase from baseline was 84x10^9/L (P=0.0173). Overall, the results of the mean change from baseline platelet count analysis using the LOCF imputation method were similar to the results of the analysis without LOCF

Overall, platelet counts increased and were sustained within normal limits in 25 of 30 patients (83%; 95% CI: 65%-94%) during the eculizumab treatment period (Table 39). Of the 13 patients with abnormal platelet count at baseline, 10 patients (77%) achieved platelet count normalization as shown in Table 39. The first occurrence of normal platelet count (≥150x10^9/L) was observed on the same day as the first eculizumab dose (Figure 14). This included patients who had normal platelet count at baseline and maintained normal platelet count as well as those who normalized their platelet count from an abnormal baseline count. Among responders, the maximum duration of platelet count normalization ranged from five to 92 weeks (32 to 646 days) after the first eculizumab dose, as of the data cut-off date

Table 39: Platelet count normalisation and first occurrence of normal platelet count from baseline through data cut-off date

	Number of Patients with Improvement/Total patients (%)		
	Platelet Count at Baseline		All Patients (N=30)
	<150×10^9/L (n=13)	≥150×10^9/L (n=17)	
Sustained Platelet Count Normalization[a] from baseline through data cut-off date	10/13 (77)	15/17 (88)	25/30 (83)
At least One Platelet Count ≥150×10^9/L from baseline through end of study involvement	12/13 (92)	17/17 (100)	29/30 (97)

[a]Platelet count being observed to be ≥150×10^9/L on at least two consecutive measurements which span a period of at least four weeks.

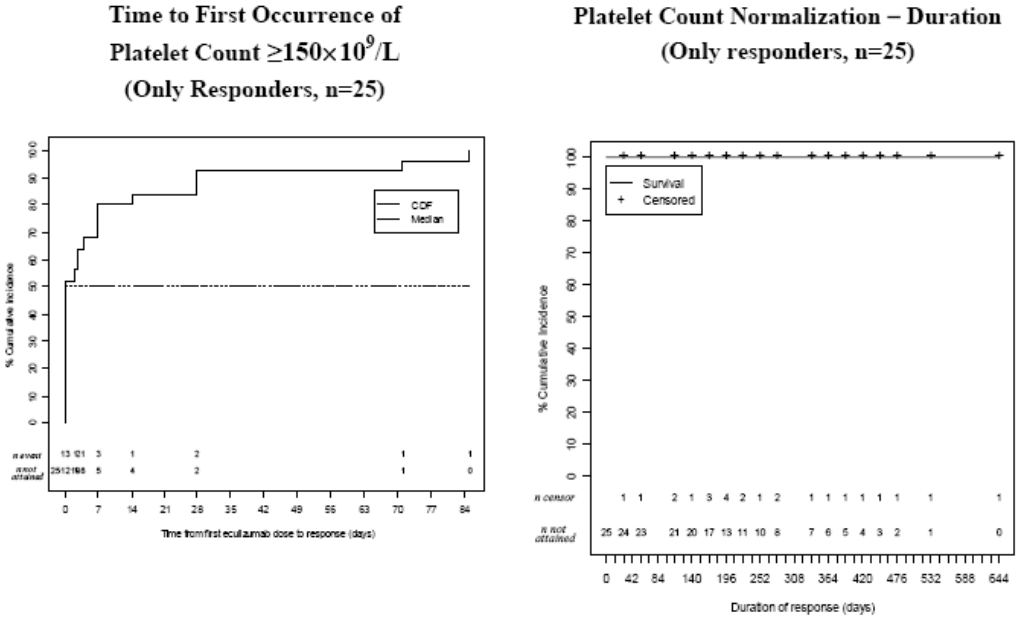


Figure 14: Platelet count normalisation – time to first occurrence and duration

2. TMA Intervention Rate

Prior to the initiation of eculizumab (within 28 days prior to the first dose), 24 of 30 (80%) patients required PT and 11 of 30 patients (37%) received dialysis for renal failure.

There were only two patients (7%) who required a TMA intervention with new dialysis during eculizumab treatment. One patient received dialysis 3 times weekly from Days 14 to 30, and another patient received dialysis on Days 18 and 19 and started receiving new dialysis three times weekly for approximately 1 month, starting on Day 48.

Dialysis was still ongoing at the time of the last record for the first patient. A total of 9 patients (30%) received a TMA intervention with PT during treatment with eculizumab.

The median TMA intervention rate significantly decreased from 0.34 PT events/patient/day to 0 PT events/patient/day. The difference in the TMA intervention rates prior to eculizumab treatment compared to the eculizumab treatment period, as assessed using the signed rank test, was statistically significant (P<0.0001).

Table 40: TMA intervention rates pre-eculizumab treatment and during eculizumab treatment from baseline through the end of study involvement

Intervention Rate	Pre-Eculizumab Treatment (N=30)[a]	During Eculizumab Treatment (N=30)[b]	*P*-value (Signed-Rank test)
Intervention rate per patient (events/patient/day) Median (Min; Max)	0.34 (0.00; 2.38)	0 (0.00; 0.41)	<0.0001
Number of patients (% of Total) with a dialysis event (pre-eculizumab treatment)[c] or new dialysis[d] (during eculizumab treatment)	11 (37)	2 (7)	N/A
Number of patients (% of Total) receiving Plasma Therapy	24 (80)	9 (30)	N/A
Number of Plasma therapies Median (Min; Max)	8 (0; 29)	0 (0; 16)	N/A

[a]Pre-treatment period for the calculation of TMA rates is from the later of the start of the current aHUS episode or twenty-eight days prior to first dose until first dose.
[b]Treatment period for the calculation of (1) PT sessions is from the first dose to the end of study involvement and (2) new dialyses is from 15 days following the first dose to the end of study involvement.
[c]One patient had imprecise dialysis information 12 days prior to the first dose. Thus, the pre-treatment period for patient is from 12 days prior to the first dose.
[d]New Dialysis events are any dialysis events that occur in patients who had no pre-treatment dialysis from 28 days prior to first dose of eculizumab to the first dose and had dialysis 15 or more days after first dose.
N/A: Not applicable.

3. TMA Event-Free Status Data

Twenty of 30 patients [67%, 95% CI: 47%-83%] achieved TMA Event-Free status. The proportion of patients achieving TMA Event-Free status appeared to be higher in patients with identified complement regulatory factor mutations or auto-antibodies (71%), as compared to patients without mutations in complement regulatory factor (44%).

As of the end of study involvement date, the median time to attain TMA Event-Free status, as assessed using the cumulative incidence, was 14 days and the median time to attain a confirmed TMA Event-Free status was 88 days. Maximum length of TMA Event-Free status was sustained for a median duration of 31 weeks (214 days) and ranged from 18 to 92 weeks (123 to 646 days). Furthermore, there was no apparent difference in the maximum number of days of TMA Event-Free status between patients with or without identified complement regulatory factor mutations or auto-antibodies

Table 41: Summary of TMA event-free status from baseline through end of study

	Number of Patients with TMA Event-Free status/Total patients n/N (%)	Maximum Duration (Days)[a]	
		n	Median (Min; Max)
All patients (N=30)	20/30 (67)	20	214 (123; 646)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=14)	11/14 (79)	11	189 (123; 646)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=16)	9/16 (56)	9	260 (127; 489)

[a]In the absence of platelet count being observed to be $<150\times10^{9}$/L or new dialysis or plasma therapy, patient is assumed to remain in TMA Event-Free state until later of last dose and end of until the end of study involvement.

Source: Table 14.2.4a

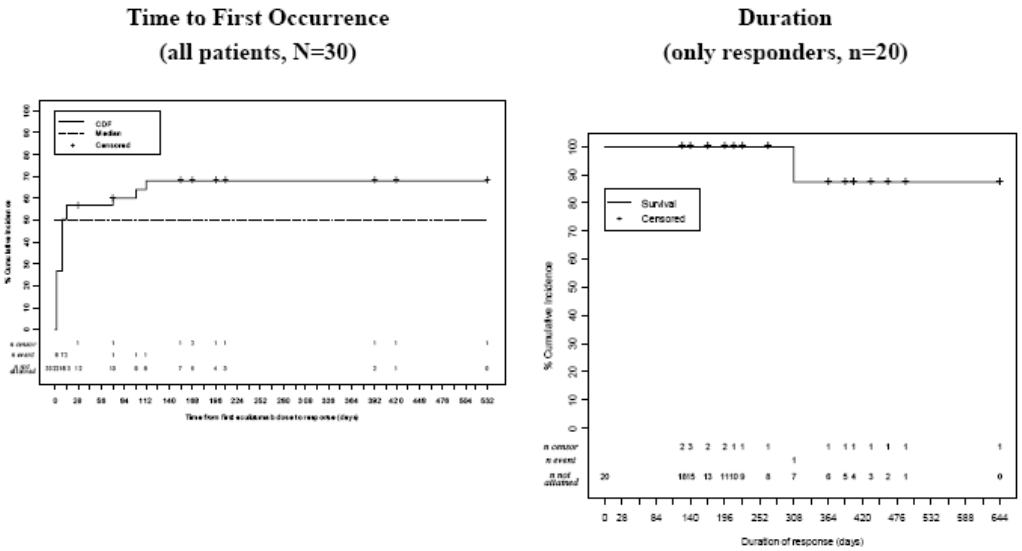


Figure 15: TMA event-free status - Time to first occurrence and duration

4. Changes in Hemoglobin

Nineteen of 30 patients (63%) showed at least an improvement in hemoglobin of 20 g/L or more during the study (Table 42). Sustained improved in hemoglobin by at least 20 g/L for at least 4 weeks was reported by 13 of 30 patients (43%; 95% CI: 25%; 63%). Patient's with or without identified complement regulatory factor mutations or auto-antibodies showed similar frequencies of sustained hemoglobin improvement.

Table 42: Improvement in haemoglobin levels ⩾ 20g/L from baseline through end of study involvement

	Number of Patients with Improvement/Total patients (%)	
	At Least One Measurement Demonstrating Improvement	Sustained[a]
Hemoglobin improvement ≥20 g/L		
All patients (N=30)	19/30 (63)	13/30 (43)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=14)	9/14 (64)	7/14 (50)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=16)	10/16 (63)	6/16 (38)

[a]Sustained is defined as two consecutive visits spanning at least four

5. LDH Being Less Than or Equal to the Upper Limit of Normal

Table 43: Frequency of LDH below the upper limit normal from baseline through end of study involvement

	Number of Patients with Improvement/Total patients (%)	
	At Least One Measurement Demonstrating Improvement	Sustained[a]
LDH ≤ULN		
All patients (N=30)	26/30 (87)	18/30 (60)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=14)	13/14 (93)	12/14 (86)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=16)	13/16 (81)	6/16 (38)

[a]Sustained is defined as two consecutive visits spanning at least four

6. Renal Function

Table 44: Proportion of patients with improvement in renal function from baseline through the date of last record stratified by complement regulatory factor mutation

	Number of Patients with Improvement/Total patients (%)	
	At Least One Measurement Demonstrating Improvement	**Sustained[a]**
eGFR improvement ≥15mL/min/1.73 m^2		
All patients (N=30)	16/30 (53)	11/30 (37)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=14)	6/14 (43)	5/14 (36)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=16)	10/16 (63)	6/16 (38)
Improvement in at Least One CKD Stage[b]		
All patients (N=30)	18/30 (60)	12/30 (40)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=14)	8/14 (57)	5/14 (36)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=16)	10/16 (63)	7/16 (44)
Creatinine decrease of at least 25% from baseline		
All patients (N=30)	20/30 (67)	12/30 (40)
Positive for Complement Regulatory Factor Mutation or Auto-Antibody (n=14)	9/14 (64)	5/14 (36)
No Identified Complement Regulatory Factor Mutation or Auto-Antibody (n=16)	11/16 (69)	7/16 (44)

[a] Sustained is defined as two consecutive visits spanning at least four weeks
[b] CKD: Including Stages 1, 2, 3a, 3b, 4 and 5
Source: Table 14.2.9.2a

Table 45: Proportion of patients with improvement in eGFR – stratified by baseline eGFR

	Number of Patients with Improvement/Total patients (%)	
	At Least One Measurement Demonstrating Improvement	Sustained[a]
eGFR improvement ≥15mL/min/1.73 m²		
All patients	16/30 (53)	11/30 (37)
Baseline eGFR <15 mL/min/1.73 m²	2/8 (25)	2/8 (25)
Baseline eGFR ≥15 mL/min/1.73 m²	14/22 (64)	9/22 (41)

[a] Sustained is defined as two consecutive visits spanning at least four weeks

7. Sponsor Assessment: Haematological Normalisation and Complete TMA Response

In this retrospective study, extent of dosing, frequency of laboratory testing and tests performed were variable. Some of the pre-specified analyses used in the two prospective studies (in particular the composite endpoints of Hematologic Normalization and complete TMA response) had important analytical limitations. Due to these limitations, a sponsor assessment was performed using criteria similar to those which were applied in the prospective studies.

Five categories of responses were used:

- Hematologic normalization: Normalization of platelet count and LDH levels in patients who had abnormal platelet counts at baseline or immediately prior to baseline. The LDH criterion was waved if no LDH measurement was reported during eculizumab therapy.
- Complete TMA response: Hematologic normalization and improvement in renal function, defined as a ≥25% decrease in serum creatinine from baseline.
- Stable biologic parameters: Stable platelet counts (no more than 25% decrease) and, stable LDH levels (no more than 25% increase) during eculizumab therapy and during the period immediately preceding eculizumab therapy while on PT.
- No response
- Not evaluable: Patients whose disease could not be evaluated due to confounding factors or concomitant disease. Reasons for the not evaluable status were recorded

Twenty patients were categorized as plasma therapy resistant (durations of current TMA manifestation <2 months) and eight patients were categorized as plasma therapy sensitive (duration of current TMA manifestations ≥ 2 months). Two patients were not categorized as either PT-resistant or PT-sensitive because they did not have evidence of active TMA manifestations at baseline. One adolescent patient who had a nephrectomy, started on eculizumab as a preparation for kidney transplant but died of complication of vascular surgery; the other pediatric patienthad a kidney transplant and started eculizumab 11 days after transplantation.

Based on sponsor assessment, ten patients achieved Haematologic Normalization and Complete TMA Response. In these 10 patients the median duration of current episode was 31 days (range 2-60). Ten other patients achieved stable biological parameters while on PT. While on eculizumab, these parameters remained stable after discontinuation of PT.

Conclusion on retrospective paediatric study (C09-001r)

Data from the retrospective study appear to demonstrate that the efficacy of eculizumab in the paediatric population is similar to that seen in adult patients. In the paediatric population, as in the adult population, there were important differences between patients with a short duration of aHUS clinical complication (similar to patients included in study C08-002A/B) and patients with long duration of clinical aHUS complication (similar to patient on chronic PT). Almost all patients exhibited a reduced TMA process without the support of plasma therapy as illustrated by the observation of platelet count normalization and the achievement of TMA event-free status (Table 2). As seen in adult patients, improvement in renal function was seen in patients with a short duration of aHUS reflecting the acute injury of the TMA process on the kidney. A long duration of current aHUS episode can lead to irreversible kidney damage and no improvement in renal function was documented despite achieving control of the TMA process in these patients.

Table 2: Key Efficacy Parameters in Pediatric Patients

	Duration of aHUS episode		All patients N=15
	< 2 months N=10	>2 months N=5	
Platelet count normalization	9 (90)	5 (100)	14 (93)
TMA event-free status	8 (80)	3 (60)	11 (73)
Complete TMA response	7 (70)	0	7 (47)
eGFR improvement ≥ 15 mL/min/1.73m^2	7 (70)	0*	7 (47)*
*one patient achieved eGFR improvement after renal transplant			

Preliminary Data from ongoing paediatric Study C10-003

In September 2010, following the recommendation of Paediatric Committee (PDCO) as written and agreed upon in the PIP, Alexion initiated a prospective study in paediatric aHUS patients from ages 1 month to less than18 years old. As of today, four patients have been accrued (data not shown).

3.3.3.4. Analysis performed across trials (pooled analyses and meta-analysis)

The MAH did not carry out any statistical integration or comparison of the two prospective studies although a comparison and analyses of results across studies has been performed.

Table 46: Change in platelet counts from baseline through week 26 and TMA event free status in subpopulations of aHUS patient-prospective studies

Subpopulation {n/n}*	C08-002A/B Point Estimate through wk 26	C08-002A/B TMA-event free	C08-003A/B Point Estimate through wk 26	C08-003A/B TMA-event free
All patients (95% CI) {17/20}	73 (40, 105)	15/17 (88 %)	5 (-17, 28)	16/20 (80 %)
Patients with PT <2 months {16/0}	82	14/16 (88 %)	NA	0/0 (NA)
Patients with PT ≥2 months {1/20}	NA	1/1 (100 %)	5	16/20 (80 %)
Patients with single or multiple CRF mutations or with anti-CRF antibodies {13/14}	76	12 /13 (92 %)	12	12/14 (86 %)
Patients without CRF mutations {4/6}	114	3/4 (75 %)	-9	4/6 (67 %)
No prior kidney transplant {10/12}	103	9/10 (90 %)	19	11/12 (92 %)
Prior kidney transplant {7/8}	63	6/7 (86 %)	-47	5/8 (63 %)
Patients with dialysis {6/2}	97	6/6 (100 %)	7	2/2 (100 %)
Patients without dialysis {11/18}	54	9/11 (82 %)	5	14/18 (78 %)
Patients in first clinical TMA manifestation {7/5}	144	6/7 (86 %)	-3	4/5 (80 %)
Patients with multiple clinical TMA manifestations {10/15}	68	9/10 (90 %)	8	12/15 (80 %)

{n/n}: number of patients in study C08-002A/B/number of patients in study C08-003A/B

Table 47: Haematologic normalisation in subpopulation of aHUS patients-prospective studies

Subpopulation	C08-002A/B n/N (%)	C08-003A/B n/N (%)
All patients, n/N (%)	13/17 (76)	18/20 (90)
Patients with PT <2 months	13/16 (81)	NA
Patients with PT ≥2 months	0/1	18/20 (90)
Patients with single or multiple CRF mutations or with anti-CRF antibodies	10/13 (77)	13/14 (93)
Patients without CRF mutations	3/4 (75)	5/6 (83)
No prior kidney transplant	8/10 (80)	12/12 (100)
Prior kidney transplant	5/7 (71)	6/8 (75)
Patients with dialysis	5/6 (83)	2 / 2 (100)
Patients without dialysis	8/11 (73)	16 / 18 (89)
Patients in first clinical TMA manifestation	5/7 (71)	4/5 (80)
Patients with multiple clinical TMA manifestations	8/10 (80)	14/15 (93)

Table 48: Complete TMA response in subpopulation of aHUS patients-prospective studies

	C08-002A/B	C08-003A/B
Subpopulation	**n/N (%)**	**n/N (%)**
All patients	11/17 (65)	5/20 (25)
Patients with PT <2 months	11/16 (69)	NA
Patients with PT ≥2 months	0/1	5/20 (25)
Patients with single or multiple CRF mutations or with anti-CRF antibodies	9/13 (69)	3/14 (21)
Patients without CRF mutations	2/4 (50)	2/6 (33)
No prior kidney transplant	7/10 (70)	4/12 (33)
Prior kidney transplant	4/7 (57)	1/8 (13)
Patients with dialysis[a]	5/6 (83)	0/2 (0)
Patients without dialysis	6/11 (55)	5/18 (28)
Patients in first clinical TMA manifestation	5/7 (71)	1/5 (20)
Patients with multiple clinical TMA manifestations	6/10 (60)	4/15 (27)

Table 49: eGFR improvement ≥ 15mL/1.73 m^2 in subpopulation of aHUS patients-prospective studies

	C08-002A/B	C08-003A/B
Subpopulation	**n/N (%)**	**n/N (%)**
All patients	8/17 (47)	1/20 (5)
Patients with PT <2 months[a]	8/16 (50)	0/0 (NA)
Patients with PT ≥2 months[b]	0/1 (0)	1/20 (5)
Patients with single or multiple CRF mutations or with anti-CRF antibodies	7/13 (54)	0/14 (0)
Patients without CRF mutations	1/4 (25)	1/6 (17)
No prior kidney transplant	7/10 (70)	0/12 (0)
Prior kidney transplant	1/7 (14)	1/8 (13)
Patient with dialysis[a]	3/6 (50)	0/2 (0)
Patient without dialysis	5/11 (45)	1/18 (6)
Patients in first clinical TMA manifestation	3/7 (43)	0/5 (0)
Patients with multiple clinical TMA manifestations	5/10 (50)	1/15 (7)

3.3.3.5. Discussion on Clinical Efficacy

To support this indication, the company presented 2 clinical trials and 1 retrospective study in aHUS patients.

Both clinical trials, Study C08-002A/B and Study C08-003A/B, share a similar design: open-label, non-randomized, single-arm multi-center, controlled clinical trial of eculizumab in adults and adolescents (between 12 to 18 years weighing ≥40 kg). They mainly differ in the studied population and in the selection of the primary endpoint, although all in all both studies assessed the same parameters. Study C08-002 included a population refractory to plasma therapies defined as aHUS patients who did not respond or insufficiently responded to, or were intolerant to aggressive PT. Study C08-003 included a less severe population stable on chronic PT.

The primary endpoint of platelet normalization is relevant to the patient and the magnitude of the observed effect (82%; 95% CI: 57%-96%) is considered clinically significant. These results are supported by the results of Haematologic Normalisation that was achieved by 76% of patients (95% CI:50-93%). Of relevance is also the accomplishment of the secondary endpoints of TMA intervention rate, TMA event free status and Complete TMA response.

The results in those patients sensitive to PT, Study 003A/B, also showed that eculizumab might also provide some benefit in this subset of patients. Outcomes from the PT-resistant study were very relevant in the context of a population which did not improve with the usual treatment (ie PT). However, the population recruited in this trial (003, PT-sensitive) achieved some clinical benefit from the PT. In this regard, it should be noted that these patients underwent a mean of 1.5 PT sessions within 7 days prior to the first dose of eculizumab and most patients had normal platelet count and normal LDH at entry. On the contrary, in the study C08-002, the patients received 5 ± 2 PT sessions in the 7 days prior to the first dose of eculizumab and all but two patients had an abnormal platelet count. Having said that, the use of eculizumab in this setting (PT-sensitive patients) could be interpreted as an alternative pharmacological therapy to PT, and also hampering further renal damage. The results from study C08-003 (PT-sensitive population) could not show outstanding results in this regard but it has to be acknowledged that the results from some patients stress some grade of improvement in the renal function and even there appear to be some data that could suggest a better prognosis in renal transplant recipients. Nonetheless, no conclusive data are available and the uncertainties on the potential long-term renal function protection remain. However, the available results in this population are considered sufficiently relevant to support a broad indication in the aHUS population.

Regarding the update from the prospective studies C08-002 and C08-003 (until 64-62 weeks), it is worth highlighting that the efficacy of Soliris, in the maintenance of the platelet count and replacement of plasma therapy in PT-sensitive patients, continues and even increases the renal outcomes with this treatment. There is no doubt that the use of eculizumab in aHUS patients is so far, an effective treatment in these patients.

Until now, there was the concern about the maintenance of the effect, but considering the data submitted by the company, a relevant clinical effect can be concluded (normalization of platelet count, maintenance of platelet levels, TMA event-free status).

The available evidence in the paediatric aHUS population shows similar results to those seen in adults. A clinically relevant benefit in the PT-resistant population is demonstrated. There is normalization in the platelet count and a real improvement in the renal function. As in adults, this clinical benefit is less pronounced in the PT-sensitive subset, since the platelet count could not be a good variable to show the efficacy in this population and the renal function is not significantly improved, given the status of the kidney at this stage of the disease. However, eculizumab has demonstrated so far to be a valid and convenient alternative to PT in the subset of PT-sensitive paediatric aHUS patients. Although further evidence in support of the potential long-term renal protection might be welcomed, the difficulties are acknowledged and the available evidence are deemed sufficiently relevant so as to support the broad claimed indication.

3.3.4. Clinical safety

The evaluation of the safety of eculizumab in the treatment of patients with aHUS is based on data from all clinical studies included in this application up to their respective data cut-off dates. The analyses of patients in the two phase 2 prospective clinical trials (C08-002A/B and C08-003A/B) forms the basis for the primary safety analysis (Table 50). These two studies accrued a total of 37 patients who received at least one dose of eculizumab. In addition, safety information on patients with aHUS treated with eculizumab outside the two prospective clinical trials will be summarized for the retrospective data collection (C09-001r). These data will be analyzed separately from the two prospective studies due to the difference in methodologic approaches and safety assessments. Safety

reported for the two prospective studies (C08-002A/B and C08-003A/B) was assessed by examination of adverse events, clinical laboratory data and vital signs. Data are reported by individual study and for the pooled data across both prospective clinical studies.

Table 50: Eculizumab-Treated Patients Included in Safety Analyses (Studies C08-002A/B and C08-003A/B)

Population	**C08-002A/B**	**C08-003A/B**	
Adults	16	15	31
Adolescents	1	5	6
Total	17	20	37

Patient exposure

The analysis of exposure was limited to exposure to eculizumab. The total duration of exposure at each dose level was calculated for each patient. This was summarized by study and presented by the following duration categories:

- < 12 weeks
- 12-<26 weeks
- ≥26 weeks

The total duration of exposure was calculated as (last dose date - first dose date +1) for each patient. For patients who received a single dose of eculizumab the exposure was set to14 days based on the known half-life of eculizumab

The median duration of treatment for patients in C08-002A/B was 38 weeks (range 2-64 weeks) and for patients in C08-003A/B was 40 weeks (range 26-52 weeks) (Table 51). Ninety-five percent of patients were treated for at least 26 weeks.

Table 51: Duration of Treatment (Studies C08-002A/B and C08-003A/B)

	C08-002A/B (N=17)	**C08-003A/B (N=20)**	**Total (N=37)**
Mean (SD), weeks	38 (19)	40 (9)	39 (15)
Median, weeks	38	40	38
Range, weeks	2-64	26-52	2-64
<12 weeks, n (%)	2 (12)	0	2 (5)
12–<26 weeks, n (%)	0	0	0
≥26 weeks, n (%)	15 (88)	20 (100)	35 (95)

Source: Study C08-002A/B CSR Study C08-003A/B CSR and Primary Tables of Safety Summary in Module 5.3.5.3

The median exposure for patients in study C09-001r was 28 weeks (range 1-94 weeks), (Table 52). Sixteen patients were treated for at least 26 weeks. In the paediatric subgroup (<12 years) most patients were treated for at least 26 weeks. Overall treatment with eculizumab was ongoing at the time of this data collection in 20 patients.

Table 52: Duration of treatment by age category

	Age Category (years)					
	<2 n=5	2-<12 n=10	<12 N=15	12 - < 18 n=4	≥ 18 n=11	Total n=30
Mean (SD), weeks	28 (27)	35 (14)	32 (19)	25 (30)	31 (29)	31 (24)
Median, weeks	16	31	29	15	24	28
Range, weeks,	4 - 70	19 - 63	4 - 70	1 - 69	2 - 94	1 - 94
<12 weeks, n (%)	2 (40)	0	2 (13)	2 (50)	3 (27)	7 (23)
12–26 weeks, n (%)	1 (20)	2 (20)	3 (20)	1 (25)	3 (27)	7 (23)
≥26 weeks, n (%)	2 (40)	8 (80)	10 (67)	1 (25)	5 (45)	16 (53)

Source: Primary Tables of Safety Summary in Module 5.3.5.3

Regarding the dose modifications, one of the 37 patients included in the two prospective studies (C08-002A/B and C08-003A/B) had a dose reduction. One patient received one 900 mg dose instead of 1200 mg during the maintenance. No other dose increases or decreases were reported. However two patients in study C08-003A/B had an infusion interrupted prior to its completion without additional dose given. One patient received 2 additional 600 mg doses of eculizumab at the time of concomitant use of PT and one patient received an additional 900 mg dose at the time of kidney transplant. For both prospective studies, most patients received doses as prescribed, within a protocol-specified interval of 14 days ± 2 days. Overall 3/145 (2%) doses during the induction phase and 21/672 (3%) during the maintenance phase were delayed. Only two patients had a dosing interval of > 9 days (dosing on day 10-12) during the induction phase due to a delay in drug delivery to the hospital. Seven patients in study C08-002A/B study and five in study C08-003A/B had dosing intervals of > 16 days (total of 21 doses). In these patients the range of dosing was 17 days to 29 days. The administration of drug to two patients was delayed because they were hospitalized for SAEs and it was delayed for 1 patient because the patient was on vacation. For the other four patients, no reason was recorded. Five patients in study C08-003A/B had dosing intervals > 16 days. For one patient, the study medication was not delivered on time for administration. It was delayed for another patient because the patient was on vacation and for an additional patient because of a train strike in the country of residence. For the other two patients, no reason was recorded.

Table 53: Change in Dosing Interval (Studies C08-002A/B and C08-003A/B)

	C08-002A/B (N=17)	C08-003A/B (N=20)	Total (N=37)
By dose			
Induction	N=65	N=80	N=145
>9 days, n (%)	3 (5)	0	3 (2)
Maintenance	N=303	N=369	N=672
>16 days, n (%)	10 (3)	11 (3)	21 (3)
By Patient	N=17	N=20	N=37
Induction			
>9 days, n (%)	2(11)	0(0)	2(5)

Maintenance			
>16 days, n (%)	7(41)	5(25)	12(32)

Source: Study C08-002A/B CSR and Study C08-003A/B CSR

Adverse events

Overview of Adverse Events in Prospective Studies

Nearly all patients experienced a treatment emergent adverse event (AE) while on study (Table 54). A total of 43% of patients had an AE that was considered by the Investigators to be study drug-related (reported as definite or probable or possible). Study drug-related AEs occurred in 59% of patients in study C08-002A/B and 30% of patients in study C08-003A/B. SAEs were reported more frequently in study C08-002A/B (88%) than in study C08-003A/B (25%)

A total of 32% of patients experienced a severe AE. Severe AEs were more commonly noted in patients enrolled in study C08-002A/B than in patients enrolled in study C08-003A/B. Five patients had a drug related SAE.

One patient from study C08-002A/B discontinued treatment because of AEs, which were not considered study drug-related.

Table 54: Overview of Adverse Events (Studies C08-002A/B and C08-003A/B)

	Number (%) of Patients		
	C08-002A/B (N=17)	C08-003A/B (N=20)	Total (N=37)
Patients with any AE	17 (100)	19 (95)	36 (97)
Patients with any drug-related AE	10 (59)	6 (30)	16 (43)
Patients with any severe AE	8 (47)	4 (20)	12 (32)
Patients with any severe drug-related AE	1 (6)	2 (10)	3 (8)
Patients with any SAE	15 (88)	5 (25)	20 (54)
Patients with any drug-related SAE	3 (18)	2 (10)	5 (14)
Patients with adverse events leading to discontinuation	1 (6)[a]	0	1 (3)
Patients with any drug-related adverse event leading to discontinuation	0	0	0

Source: Primary Tables of Safety Summary in Module 5.3.5.3

[a] A second patient was reported with an AE of Lupus Erythematosus which was counted as a protocol violation rather than an AE leading to discontinuation.

Nearly all patients experienced at least one AE. All adverse events reported in at least 10% of patients are included in Table 55. Overall, 73% of patients reported gastrointestinal disorders, with the most frequent individual AEs being diarrhea (32%) and vomiting (22%). Although not as frequent, nausea (19%) and abdominal pain (11%) were also reported. Other frequently reported AEs included headache (30%), anemia (24%), and hypertension (24%). Events classified as infections and infestations occurred in 65% of patients, with nasopharyngitis occurring in 22% and upper respiratory tract and urinary tract infections occurring in 19% and 16%, respectively. General disorders and administration site conditions occurred in 51% of patients. Musculoskeletal and nervous system

disorders both occurred in 41% of patients. Vascular disorders were reported in 41% of patients, and respiratory, thoracic and mediastinal disorders were reported in 30% of patients.

A total of 30% of patients had a severe AE (Table 55). Overall, with the exception of hypertension (5% of patients), each adverse event classified as severe occurred in one patient.

Table 55: Adverse Events Reported in >10% of Patients and All Severe AEs: Most Severe per Patient (Studies C08-002A/B and C08-003A/B)

	Number (%) of Patients					
Body system	**C08-002 (n=17)**		**C08-003 (n=20)**		**Total (n=37)**	
	All	**Severe**	**All**	**Severe**	**A**	**S**
Patients with at least 1 AE	17 (100)	8 (47)	19 (95)	4 (20)	36 (97)	12 (32)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	10 (59)	1 (6)	7 (35)	0	17 (46)	1 (3)
Anemia	6 (35)	1 (6)	3 (15)	0	9 (24)	1 (3)
Leukopenia	4 (24)	0	2 (10)	0	6 (16)	0
EAR AND LABYRINTH DISORDERS	1 (6)	0	3 (15)	0	4 (11)	0
Vertigo	1 (6)		3 (15)		4 (11)	
GASTROINTESTINAL DISORDERS	12 (71)	0	15 (75)	2 (10)	27 (73)	2 (5)
Abdominal Pain	0	0	4 (20)	0	4 (11)	0
Diarrhea	6 (35)	0	6 (30)	1 (5)	12 (32)	1 (3)
Nausea	4 (24)	0	3 (15)	0	7 (19)	0
Peritonitis	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Vomiting	5 (29)	0	3 (15)	1 (5)	8 (22)	1 (3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10 (59)	1 (6)	9 (45)	0	19 (51)	1 (3)
Fatigue	3 (18)	1 (6)	1 (5)	0	4 (11)	1 (3)
Ooedema, peripheral	3 (18)	0	1 (5)	0	4 (11)	0
Pyrexia	3 (18)	0	1 (5)	0	4 (11)	0
IMMUNE SYSTEM DISORDERS	1 (6)		5 (25)		6 (16)	
INFECTIONS AND INFESTATIONS	11 (65)	0	13 (65)	0	24 (65)	0
Nasopharyngitis	1 (6)	0	7 (35)	0	8 (22)	0
Upper respiratory tract infection	4 (24)	0	3 (15)	0	7 (19)	0
Urinary tract infection	4 (24)	0	2 (10)	0	6 (16)	0
METABOLISM AND NUTRITION DISORDERS	8 (47)	0	3 (15)	0	11 (30)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	10 (59)	1 (6)	5 (25)	0	15 (41)	1 (3)
Pain in extremity	1 (6)	0	3 (15)	0	4 (11)	0

Body system	Number (%) of Patients					
	C08-002 (n=17)		C08-003 (n=20)		Total (n=37)	
	All	Severe	All	Severe	A	S
Systemic lupus erythematosus	1 (6)	1 (6)	0	0	1 (3)	1 (3)
NERVOUS SYSTEM DISORDERS	11 (65)	3 (18)	4 (20)	0	15 (41)	3 (8)
Convulsion	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Headache	7 (41)	1 (6)	4 (20)	0	11 (30)	1 (3)
Reversible posterior leukoencephalopathy syndrome	1 (6)	1 (6)	0	0	1 (3)	1 (3)
PSYCHIATRIC DISORDERS	6 (35)	0	1 (5)	0	7 (19)	0
Insomnia	4 (24)	0	1 (5)	0	5 (14)	0
RENAL AND URINARY DISORDERS	7 (41)	1 (6)	4 (20)	1 (5)	11 (30)	2 (5)
Renal failure, chronic	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Renal impairment	4 (24)	1 (6)	2 (10)	0	6 (16)	1 (3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (35)	0	5 (25)	1 (5)	11 (30)	1 (3)
Cough	2 (12)	0	3 (15)	0	5 (14)	0
Pharyngolaryngeal pain	1 (6)	0	4 (20)	0	5 (14)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (24)	0	3 (15)	0	7 (19)	0
VASCULAR DISORDERS	9 (53)	3 (18)	6 (30)	2 (10)	15 (41)	5 (14)
Accelerated hypertension	2 (12)	0	0	0	2 (5)	0
Hypertension	4 (24)	2 (12)	5 (25)	0	9 (24)	2 (5)
Hypotension	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Malignant hypertension	2 (12)	1 (6)	0	0	2 (5)	1 (3)

Source: Study C08-002A/B CSR and Study C08-003A/B CSR and Primary Tables of Safety Summary in Module 5.3.5.3

Regarding the retrospective study, twenty two of the 30 patients included in study C09-001r experienced at least one AE. Adverse events reported in at least 10% of patients, and selected AEs reported in less than 10% of patients are included in Table 56. Overall, 57% of patients reported infections, with the most frequent individual AEs being upper respiratory tract infection (17%), nasopharyngitis and flu (10% each). Gastrointestinal disorders occurred in 40% of patients, with the most frequent events reported as diarrhea (27%) and vomiting (23%). Although not as frequent, abdominal pain (10%) was also reported. General disorders occurred in 40% of patients, with pyrexia reported in 30% of patients. Respiratory disorders both occurred in 37% of patients, with cough (23%) and nasal congestion (13%) being the most frequently-reported events.

Table 56: Adverse Events Reported in ≥10% of Patients (Study C09-001r)

	n (%), N=30
Patients with at least 1 AE	22 (73)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	6 (20)
Anemia	3 (10)
CARDIAC DISORDERS	6 (20)
Tachycardia	4 (13)
EYE DISORDERS	5 (17)
GASTROINTESTINAL DISORDERS	13 (43)
Abdominal pain	3 (10)
Diarrhea	8 (27)
Nausea	3 (10)
Vomiting	7 (23)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	12 (40)
Pyrexia	9 (30)
INFECTIONS AND INFESTATIONS	18 (60)
Influenza	3 (10)
Nasopharyngitis	3 (10)
Upper respiratory tract infection	6 (20)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (10)
INVESTIGATIONS	7 (23)
METABOLISM AND NUTRITION DISORDERS	8 (27)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	6 (20)
NERVOUS SYSTEM DISORDERS	11 (37)
Headache	5 (17)
PSYCHIATRIC DISORDERS	7 (23)
Insomnia	3 (10)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	11 (37)
Cough	7 (23)
Nasal congestion	4 (13)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	7 (23)
VASCULAR DISORDERS	3 (10)
Hypertension	2 (7)

Source: Study C08-002A/B CSR and Study C08-003A/B CSR and Primary Tables of Safety Summary in Module 5.3.5.3

Drug-Related Adverse Events in Prospective Controlled Studies

Adverse events considered related to study drug by the Investigators were reported in 43% of patients in the two prospective controlled studies. Leukopenia (11%) was the most commonly reported study drug-related AE. Study drug-related AEs were reported in at least 5% of patients and all severe and drug-related AEs are included in Table 57.

Three study drug-related events (peritonitis, hypertension and vein disorder) were severe.

Table 57: Drug-Related Adverse Events reported in ≥5% of Patients and All Severe AEs– Most Severe per Patient (Studies C08-002A/B and C08-003A/B)

	Number (%) of Patients					
	C08-002 (n=17)		C08-003 (n=20)		Total (n=37)	
Body system	All	Severe	All	Severe	A	S
Patients with at least 1 drug-related AE	10 (59)	1 (6)	6 (30)	2 (10)	16 (43)	3 (8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (12)	0	3 (15)	0	5 (14)	0
Leukopenia	2 (12)	0	2 (10)	0	4 (11)	0
Lymphopenia	0	0	2 (10)	0	2 (5)	0
EAR AND LABYRINTH DISORDERS	1 (6)	0	1 (5)	0	2 (5)	0
Vertigo	1 (6)	0	1 (5)	0	2 (5)	0
GASTROINTESTINAL DISORDERS	2 (12)	0	1 (5)	1 (5)	3 (8)	1 (3)
Nausea	2 (12)	0	0	0	2 (5)	0
Peritonitis	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Vomiting	2 (12)	0	0	0	2 (5)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (12)	0	1 (5)	0	3 (8)	0
INFECTIONS AND INFESTATIONS	3 (18)	0	1 (5)	0	4 (11)	0
INVESTIGATIONS	2 (12)	0	0	0	2 (5)	0
NERVOUS SYSTEM DISORDERS	2 (12)	0	2 (10)	0	4 (11)	0
Headache	1 (6)	0	2 (10)	0	3 (8)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (12)	0	1 (5)	0	3 (8)	0
VASCULAR DISORDERS	3 (18)	1 (6)	1 (5)	1 (5)	4 (11)	2 (5)
Accelerated hypertension	2 (12)	0	0	0	2 (5)	0
Hypertension	1 (6)	1 (6)	0	0	1 (3)	1 (3)

Source: Study C08-002A/B CSR and Study C08-003A/B CSR and Primary Tables of Safety Summary in Module 5.3.5.3

Deaths

No deaths were reported in the C08-002A/B and C08-003A/B prospective studies. There were two deaths in study C09-001r. One thirteen year old female received eculizumab in preparation for a kidney transplant. She underwent angioplasty for severe carotid artery stenosis which was complicated by artery dissection. She subsequently developed a stroke and died 5 days after the surgical procedure. The second patient was a 47 year-old male whose cause of death was attributed to multi-organ failure due to uncontrolled graft versus host disease and pulmonary aspergillosis.

Other Serious Adverse Events in Prospective Studies

Serious AEs were reported in 20 (54%) patients treated in studies C08-002A/B and C08-003A/B. They were considered drug-related in four patients (3 in study C080-002A/B and a single patient in study C08-003A/B). SAEs reported in greater than 5% of patients are reported in Table 58. There were more SAEs reported for patients enrolled in study C08-002A/B (88%) than for patients enrolled in study C08-003A/B (35%). The most commonly reported SAEs were hypertension, infections and renal impairment including renal failure, renal impairment and hematuria. There were five SAEs of infection consisting of upper respiratory infections (two patients), varicella infection (one patient), gastroenteritis (one patient) and Clostridium difficile diarrhea (one patient). All infections were considered by the investigator to be unrelated to study drug. Of note, the patient with varicella infection had a history of varicella zoster infection. All patients recovered after appropriate therapy.

There were 3 SAEs related to central nervous system disorders. One patient had a seizure, one patient had reversible posterior leukoencephalopahy syndrome and one had a headache. Seizure and reversible posterior leukoencephalopathy were attributed to underlying hypertension. All patients recovered.

The four drug-related SAEs consisted of accelerated hypertension (reported in two patients in study C08-002A/B), hypertension (one patient in study C08-002A/B) and peritonitis (one patient in study C08-003A/B).

Table 58: Other Serious Adverse Events Reported in ≥5% and All Severe SAEs (Studies C08-002A/B and C08-003A/B)

	Number (%) of Patients					
	C08-002 (n=17)		C08-003 (n=20)		Total (n=37)	
Body system	All	Severe	All	Severe	A	S
Patients with at least one SAE	15 (88)	6 (35)	5 (25)	3 (15)	20 (54)	9 (24)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (12)	0	0	0	2 (5)	0
CARDIAC DISORDERS	2 (12)	0	0	0	2 (5)	0
GASTROINTESTINAL DISORDERS	1 (6)	0	1 (5)	1 (5)	2 (5)	1 (3)
Peritonitis	0	0	1 (5)	1 (5)	1 (3)	1 (3)
HEPATOBILIARY DISORDERS	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Cholelithiasis	1 (6)	1 (6)	0	0	1 (3)	1 (3)
INFECTIONS AND INFESTATIONS	4 (24)	0	1 (5)	0	5 (14)	0
Clostridium difficile colitis	0	0	1 (5)	0	1 (3)	0

	Number (%) of Patients					
	C08-002 (n=17)		C08-003 (n=20)		Total (n=37)	
Body system	All	Severe	All	Severe	A	S
Gastroenteritis	1 (6)	0	0	0	1 (3)	0
Upper respiratory tract infection	2 (12)	0	0	0	2 (5)	0
Varicella	1 (6)	0	0	0	1 (3)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (12)	1 (6)	0	0	2 (5)	1 (3)
Systemic lupus erythematosus	1 (6)	1 (6)	0	0	1 (3)	1 (3)
NERVOUS SYSTEM DISORDERS	2 (12)	2 (12)	1 (5)	0	3 (8)	2 (5)
Convulsion	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Reversible posterior leukoencephalopathy syndrome	1 (6)	1 (6)	0	0	1 (3)	1 (3)
RENAL AND URINARY DISORDERS	4 (24)	1 (6)	1 (5)	1 (5)	5 (14)	2 (5)
Renal failure, chronic	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Renal impairment	3 (18)	1 (6)	0	0	3 (8)	1 (3)
VASCULAR DISORDERS	6 (35)	3 (18)	2 (10)	2 (10)	8 (22)	5 (14)
Accelerated hypertension	2 (12)	0	0	0	2 (5)	0
Hypertension	2 (12)	2 (12)	0	0	2 (5)	2 (5)
Hypotension	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Malignant hypertension	2 (12)	1 (6)	0	0	2 (5)	1 (3)
Vein disorder	0	0	1 (5)	1 (5)	1 (3)	1 (3)

Source: Study C08-002A/B CSR and Study C08-003A/B CSR and Primary Tables of Safety Summary in Module 5.3.5.3

Discontinuations.

In study C08-002A/B, two patients discontinued early before completing the 26 week treatment period (one patient met the exclusion criteria and another discontinued because of an adverse event unrelated to study drug). In addition, two other patients in study C08-002A/B discontinued eculizumab treatment after completing the 26 week treatment period; one patient with an identified MCP mutation was doing well at last follow-up 8 weeks after discontinuation, and the other patient was lost to follow-up although this patient experienced sustained haematologic normalization, TMA event free status and complete TMA response from day 14-182 while on eculizumab.

In study C08-003A/B, there were no early discontinuations and one patient discontinued after receiving 16 doses of eculizumab and completing the 26 week treatment period. Following discontinuation and completion of the protocol mandated 8 week follow-up period, this patient experienced a severe TMA complication 80 days after discontinuation (personal communication from treating physician). Platelet count dropped by more than 25% from baseline and more than 50% from peak while on eculizumab and worsening of renal function with a nephrotic syndrome. This patient

reinitiated eculizumab treatment, did not require further PT and haematologic parameters normalized and renal function returned to baseline. The patient remains on eculizumab and without PT.

Table 59: Outcome Post-Discontinuation of Eculizumab (Studies C08-002A/B and C08-003A/B)

Patient ID	Duration of eculizumab	Reason for discontinuation	Outcome after discontinuation
A*	1 dose	Patient ineligible	NA
B	4 weeks	AE unrelated to eculizumab	NA
C	26 weeks	Completed 26 weeks of eculizumab	Doing well after 8 weeks follow-up period
D	26 weeks	Completed 26 weeks of eculizumab	Lost-to-follow-up
E	26 weeks	Completed 26 weeks of eculizumab	Severe TMA complications 80 days post discontinuation

* Patient A was diagnosed with SLE within the first week of enrollment and received one dose of eculizumab

Source: Study C08-002A/B CSR and Study C08-003A/B CSR, Tabulation of Key Clinical Laboratory Parameters and Individual Patients Summaries

In study C09-001r, thirteen patients discontinued eculizumab treatment. Of these 13 patients, four patients initially received only a single dose. One patient received only a single dose of eculizumab while three others received a single dose and then were restarted with eculizumab treatment after some period of dosing interruption ranging from 30 days to 1 year. One of these three experienced two dosing interruptions.

The patient in the C09-001r study that received only a single dose of eculizumab experienced a greater than 25% drop in platelet count from baseline and experienced a rapid and severe TMA complication within 30 days after discontinuation leading to chronic dialysis and graft failure. Three other patients in study C09-001r received an initial dose of eculizumab, experienced a severe TMA complication, and required restart of eculizumab treatment.

Two other patients had a treatment interruption after one dose of eculizumab. Both of them experienced a rapid decline in platelet count and an increase in creatinine leading to severe TMA complication (33 days and 8 weeks, respectively) following discontinuation. Both patients were restarted on eculizumab although one of them discontinued again and dropped the platelet count by nearly 30% from peak and subsequently discontinued after rapid progression to ESRD.

The third patient received a single dose of eculizumab, was observed to have a decline of platelet count of approximately 35% within 12 weeks post dose, and experienced a new severe TMA complication after approximately 1 year and required intubation with mechanical ventilation for respiratory distress. This patient was restarted on eculizumab and achieved platelet count normalization and improvement in both hemoglobin and renal function. Dosing was again interrupted due to patient non-compliance and the patient's platelet count dropped almost 80% from peak and the patient experienced a new severe TMA complication 53 days after the prior dose. Dosing was restarted and this patient remains on eculizumab and to date is free of PT and dialysis.

There were two additional patients who discontinued eculizumab within five days of the last eculizumab dose. Any TMA complication occurring within one week of the eculizumab last dose is not considered a potential severe TMA complication post eculizumab since the complication actually occurred prior to the missed dose.

Seven other patients in the C09-001r study also discontinued eculizumab treatment (duration ranged between 7 days and 168 days). Of these seven patients, two died and the cause of death was not considered drug related. Two other patients were on chronic dialysis prior to eculizumab and remained on chronic dialysis after discontinuation of eculizumab. In the remaining 3 patients there was no evidence of clinical complication of TMA after follow-up ranging from 5 to 221 days.

Table 60: Patients discontinuing eculizumab treatment (Study C09-001r)

Patient ID	Duration of eculizumab	Outcome after discontinuation
a	1 day	Severe complication of TMA with decrease in platelet count and increase in creatinine within 30 days of discontinuation. End stage renal disease, graft failure and chronic dialysis
b	1 day and then Days 33 – 39	Severe TMA complication with decrease in platelet count, increased creatinine after each discontinuation – progression to ESRD
c	1 day and then Days 70 – 279	Severe complication of TMA with decrease in platelet count and increase in creatinine within 8 weeks. Restarted and still on eculizumab at time of data collection
d	1 day and then Days 349 - 460	Severe TMA complications after less than 1 year with decrease in platelet count and respiratory distress requiring mechanical ventilation. Second brief interruption leading to significant drop in platelet count and increase in creatinine. Currently on eculizumab
e	66 days	Severe complication of TMA with decrease in platelet count concomitant with infection 5 days post discontinuation. Continue on chronic dialysis
f	28 days	Severe complication of TMA with decrease in platelet count concomitant with infection.
g	70 days	death on study
h	83 days	death on study due to worsening of graft versus host disease
i	7 days	On chronic dialysis before and after eculizumab
j	20 days	On chronic dialysis. Normalization of platelet count but no change in renal function
k	160 days	No reported severe medical complication 221 days post dose.
l	133 days	No reported severe medical complication 42 days post last dose of eculizumab.
m	168 days	Discontinuation 5 days prior to data collection, no data available

Source: Study C09-001r CSR, Tabulation of Key Clinical Laboratory Parameters and Individual Patients Summaries

Analysis of Adverse Events by Organ System or Syndrome

Neisseria meningitidis Infections

Description of All Cases of Meningococcal Infection

Patients treated with eculizumab are at an increased risk for the development of infection caused by the encapsulated bacteria Neisseria meningitidis. In the two prospective studies (studies C08-002A/B and C08-003A/B) and the retrospective study (study C09-001r), no instances of meningococcal infection have been reported.

As of 30 Nov-2010, there had been 18 reported cases of Neisseria meningitidis among patients treated with eculizumab, three from clinical trials and 15 during the post marketing experience (Table 61). The first case in clinical trial occurred in an unvaccinated non-PNH patient. Two other cases were reported in clinical studies in vaccinated PNH patients. During the post marketing period, 15 cases were reported including one aHUS patient. This patient is included in the retrospective study C09-001r but the infection occurred after the data collection.

Table 61: Number of Meningococcal Infections Associated with Eculizumab Use

	No. of patients
Clinical trials	3
aHUS	0
PNH	2
Non-PNH	1
Post marketing reports	15
aHUS	1
PNH	13
Other	1
Total	18
Year of diagnosis	
2001	1
2006	2
2007	1
2008	3
2009	3
2010	8

The number of cases progressively increased as the total number of patients exposed to Soliris increased. The rate of meningococcal infections has not changed from the clinical trial experience and throughout the post-marketing experience with a consistent rate of less than 0.5 cases per 100 patient years.

Consistent with the epidemiology of both PNH and Neisseria infections, the majority of patients who developed meningococcal infections were young adults with a median age of 23 years (Table 62). Of the 18 patients, 17 were adults and only one of these adults was older than 30 years (actual age of 54 years). To date there has been a single report of meningococcal infection in an adolescent patient and none in the pediatric population. Most patients were female and PNH was the underlying diagnosis in 15 patients. One 19-year-old aHUS patient treated outside the clinical trials developed a meningococcal infection 18 months after starting treatment with eculizumab. This patient is included in study C09-001r but the meningococcal infection occurred after the data collection.

Table 62: Baseline Characteristics of Patients with Meningococcal Infections

Age (years)	
Median	23

Range	15-54
No. of patients	
Adult, n	17
<30 years, n	16
Adolescent, n	1
Pediatric, n	0
Sex	
Male, n	6
Female, n	12
Indication	
PNH, n	15
aHUS, n	1
Other, n	2

One patient who developed meningococcal infection was treated with eculizumab prior to the initiation of the PNH program and the current risk management program. All other 17 patients who developed a meningococcal infection were vaccinated with a meningococcal vaccine according to local availability (Table 63). Eight of these patients received a tetravalent vaccine (Menactra, Menomune or Meningovax), six received a vaccine covering either Neisseria subtype C or A/C, and three patients received an unknown vaccine type. Thirteen of the 18 patients who developed infections underwent subtyping of N. meningitidis. The predominant subtype was B (7 patients). One patient had an infection caused by subtype C and another patient's infection was caused by subtype Y. These two infections occurred in patients who were vaccinated with Menactra which includes both serotypes in the target coverage.

In all other patients, the infection was caused by an N. meningitidis subtype not covered by the vaccine provided. In most patients, the infection occurred early after the initiation of eculizumab treatment with a median of 5 months. In five of the 18 patients, infection occurred more than 1 year after the initiation of eculizumab. The longest duration between eculizumab initiation and infection was 5 years in a patient who was revaccinated at a time consistent with the manufacturer's guidance.

Table 63: Vaccination and Infection Type

	n
Meningococcal Vaccination	
Menactra	4
Menomune	2
Mencevax (AC)	4
Meningovax	2
Other (C and AC)	2
Unknown	3
None	1*
***N. Meningitidis* subtype**	
A	1
B	7
C	1
Y	1
X	1
W	2
Unknown	5
Time from first dose of Soliris to infection	
Median	5 months
Min, Max	5 wks – 5 years
<3 months	4
3 - <6 months	6
6 -<12 months	3
≥12 months	5

*Prior to the initiation of PNH and aHUS development program

Fourteen of these 18 patients with meningococcal infection fully recovered (Table 64). Of those fourteen patients, nine resumed treatment with eculizumab without further problem. One patient who was not vaccinated recovered with neurological sequelae; this patient was the first to be diagnosed with meningococcal infection in the context of a clinical study. There were three meningococcal infection-related fatalities in PNH patients. The age of these patients ranged from 20 to 24 years. Two had received a bivalent meningococcal vaccine and one had received a tetravalent vaccine. Fatal infections were due to N. meningitidis type B in two patients and type X in one. The time from the beginning of eculizumab treatment to the outbreak of infection was 5 months in 2 patients and 10.5 months in the third patient. Of the 18 patients who developed meningococcal infection, six remain on Soliris without further problem, 9 discontinued Soliris, and information is not available for the remaining 3 patients.

Table 64: Outcome of Meningococcal Infections

	No of patients
Outcome of infection	
Recovered	14
Recovered with sequelae	1
Death	3
Soliris treatment	
Discontinued	9
Ongoing	6
Unknown	3

Prophylactic Antibiotics

To decrease the risk of possible infection, all patients were to be vaccinated with a meningococcal vaccine at least 14 days before his or her first eculizumab dose. In study C08-002A/B, because of the rapid and progressive nature of the aHUS, most patients required an immediate initiation of eculizumab treatment in order to prevent further severe TMA complications. Consequently, 14 patients were treated with eculizumab prior to the end of the 14 day post-vaccination period. Ten patients were vaccinated within 14 days before the first dose and four patients were vaccinated after the first dose. These 14 patients received prophylactic antibiotics until at least 14 days after the vaccination (Table 65). Two patients received long-term antibiotic prophylaxis with an oral penicillin. In these two patients, antibiotic prophylaxis was still ongoing at the time of data cut-off. The most common prophylactic antibiotics administered were quinolones and beta lactams (penicillin and cephalosporins).

Table 65: Patients Receiving Antibiotic Prophylaxis for Neisseria meningitidis (Study C08-002A/B)

Patient number	Day of vaccination relative to first dose of eculizumab	Duration of prophylaxis (days)	Antibiotics
1	-13	112 (day -64-47)	Sulfamethoxazole-trimethoprim
2	-13	15 (day -1-13)	Amoxicillin
3	-7	18 (day -3-14)	Ciprofloxacin
4	-6	14 (day 0-13)	Rifampin
5	-6	Ongoing	Penicillin V
6	-3	14 (day -3-10)	Rifampin
7	-1	155 (day 0-154)	Oracillin
8	0	13 (day 0-12)	Ciprofloxacin
9	0	19 (day 0-18)	Amoxicillin
10	0	14 (day 0-13)	Ciprofloxacin
11	1	15 (day 0-14)	Ciprofloxacin
12	1	Ongoing	Oracillin

Patient number	Day of vaccination relative to first dose of eculizumab	Duration of prophylaxis (days)	Antibiotics
13	2	14 (day 3-16)	Amoxicillin clavulanate
14	85	99 (day 0- 98)	Cefdinir

In study C08-003A/B, two patients were treated with eculizumab prior to the 14 days post- vaccination period. These two patients received prophylactic antibiotics until at least 14 days after the vaccination and antibiotic prophylaxis is still ongoing in one of them (Table 66).

Table 66: Patients Receiving Antibiotic Prophylaxis for Neisseria meningitidis (Study C08-003A/B)

Patient number	Day of vaccination	Duration of prophylaxis (days)	Antibiotics received
15	6	Ongoing	Roxithromycin
16	0	15 (day 0-14)	Amoxicillin

In the retrospective study C09-001r, 29/30 patients were vaccinated against N. meningitidis and 13 of those 29 patients were vaccinated at least 14 days prior to eculizumab. One two month-old patient was not vaccinated as there is no current recommendation for meningococcal vaccine in this age group. Of the 17 patients who were not vaccinated, or who were vaccinated less than 14 days prior to eculizumab, 15 patients (9 paediatric patients and 6 adults) received antibiotic prophylaxis (Table 67). In patients below the age of 2, three patients received a meningococcal vaccine and prophylactic antibiotics, one receive only prophylactic antibiotics and one received only a meningococcal vaccine. Antibiotic prophylaxis was still ongoing in four of these patients at the time of data cut-off. All three patients aged between 2 and <5 years received a meningococcal vaccination and two of them received antibiotic prophylaxis which was ongoing at the time of data cut-off in one of these patients. All seven patients between the age of 5 and 12 received a meningococcal vaccine and two of them also received antibiotic prophylaxis. In one patient in this age group, eculizumab was started 12 days after vaccination but no antibiotic prophylaxis was given. Six adult patients received antibiotic prophylaxis. In one patient, antibiotic prophylaxis was not started although meningococcal vaccination occurred only 10 days prior to the initiation of eculizumab. The choice of antibiotic used during prophylaxis was guided by local practices.

Table 67: Patients Receiving Antibiotic Prophylaxis for Neisseria meningitidis (Study 09-001r)

Patient number	Age	Day of vaccination	Duration of prophylaxis	Antibiotics received
17	0.2	Not vaccinated	Ongoing	Amoxicillin
18	0.6	-1	Ongoing	Amoxicillin
19	1	-3	14 days (Day 2-15)	Ciprofloxacin
20	1	0	Ongoing	Penicillin
21	2	-2	Ongoing	Sulfamethoxazole trimethoprim
22	4	-4	Ongoing	Amoxicillin
23	6	0	15 days (Day 8-23)	Ciprofloxacin

24	8	-12	NA	None
25	10	-1	15 days	Penicillin V
26	18	-10	NA	None
27	22	3	Ongoing	Sulfamethoxazole
28	29	2	232 Days	Oracillin
29	42	-4	Ongoing	Sulfamethoxazole trimethoprim, Ciprofloxacin
30	47	-1	86 Days	Ciprofloxacin, Pipericillin / tazobactam*
31	51	-7	30 days (Day 0 -30)	Ampicillin
32	31	27	1 day (Day 14)	Benzathine benzylpenicillin
33	19	84	144 (Day 0 – 144)	Amoxicillin

* Antibiotics given for active infection

Other Serious Infections

Prospective Studies

Table 68: Number of other serious infections

	Number (%) of Patients			
	All Events		Serious Events	
	Any Severity	Severe	Any Severity	Severe
All events	24 (65)	0	5 (14)	0
BK virus infection	1 (3)	0	0	0
Bronchitis	1 (3)	0	0	0
Campylobacter infection	1 (3)	0	0	0
Clostridium difficile colitis	1 (3)	0	1 (3)	0
Escherichia urinary tract infection	1 (3)	0	0	0
Gastroenteritis	2 (5)	0	1 (3)	0
Genital herpes	1 (3)	0	0	0
Herpes zoster	2 (5)	0	0	0
Impetigo	1 (3)	0	0	0
Nasopharyngitis	8 (22)	0	0	0
Pharyngitis	1 (3)	0	0	0
Pneumonia	1 (3)	0	0	0
Rhinitis	1 (3)	0	0	0
Sinusitis	2 (5)	0	0	0
Tooth abscess	1 (3)	0	0	0
Tracheobronchitis	1 (3)	0	0	0
Upper respiratory tract infection	7 (19)	0	2 (5)	0
Urinary tract infection	6 (16)	0	0	0
Urinary tract infection bacterial	1 (3)	0	0	0
Varicella	1 (3)	0	1 (3)	0

Viral pharyngitis	1 (3)	0	0	0

Source: Primary Tables of Safety Summary in Module 5.3.5.3

Regarding the retrospective study, (study C09-001r) 18 of the 30 patients had an infection. Overall, the pattern of infections was similar to what was observed in the prospective studies and there was no apparent increased risk of infection by encapsulated bacteria. Upper respiratory tract infections were noted in six patients, and influenza and nasopharyngitis were noted in three patients each. The rate of infections and the pattern of infections were similar across the various age groups. Sixty seven percent of paediatric patients had at least one infection. The most common were respiratory infections and otitis. Three of them had a catheter-related infection.

Hypertension

Hypertension is a common problem in aHUS patients. With progressive kidney damage related to an ongoing TMA process, most aHUS patients develop hypertension which can become severe and commonly requires aggressive use of multiple antihypertensive drugs. Thirty three patients, or 89%, (15 in study C08-002A/B and 18 in study C08-003A/B) were on various antihypertensive drugs prior to enrolling in this aHUS development program.

Eculizumab treatment of patients with a different form of a genetic uncontrolled complement activation disorder, PNH, has been reported to be associated with significant reductions in arterial and diastolic pressure compared to placebo-treated PNH patients. In patients with PNH, this reduction in systemic arterial pressure has been related to inhibition of complement activation and the subsequent increase in nitric oxide levels.

In prospective studies C08-002A/B and C08-003A/B, thirteen (35%) patients experienced at least one hypertension-related event including six SAEs (Table 69). Although the majority of these events were related to worsening of hypertension while on eculizumab, these hypertension events were generally mild or moderate in severity and generally determined to be unrelated to study drug. In three patients (8%) these events were considered severe (hypertension in two and malignant hypertension in one). Three events (accelerated hypertension in two patients and severe hypertension in one patient) were considered drug related.

Table 69: Hypertension-Related Events by Preferred Term (Studies C08-002A/B and C08-003A/B)

	Number (%) of Patients		
	C08-002A/B N=17	**C08-003A/B** N=20	**Total** N=37
Patients with at least 1 hypertension event	8 (47)	5 (25)	13 (35)
Hypertension	4 (24)	5 (25)	9 (24)
Worsening of hypertension[c]	3 (18)	4 (20)	7[a] (19)
Arterial hypertension	1 (6)	0	1 (3)
Increase of hypertension[c]	1 (6)	0	1 (3)
Severe hypertension[c]	1(12)	0	1[b] (3)
Hypertension	0	1 (5)	1 (3)
Accelerated hypertension	2 (12)	0	2[b] (5)
Malignant hypertension	2 (12)	0	2[b] (5)

a: one event was also classified as SAE

b: each event also classified as SAE
c: Worsening of hypertension includes 2 patients with other reported terms (increase of hypertension and severe hypertension)
Source: Primary Tables of Safety Analyses in Module 5.3.5.3

Table 70: Hypertension-Related Events in Subgroup (Studies C08-002A/B and C08-003A/B)

	Number (%) of Patients		
	C08-002A/B N=17	**C08-003A/B** N=20	**Total** N=37
All hypertension related events	8 (47)	5(25)	13 (37)
Hypertension- related events by prior history of hypertension			
History of hypertension	8/13 (62)	5/18 (27)	13/31 (42)
No history of hypertension	0/4	0 /2	0 /6
Hypertension related events by age category			
Age <18 years	0/1	1/5	1/6
Age 18-45 years	8/13 (62)	2/10 (20)	10/23 (43)
Age >45 years	0/3	2/5 (40)	2/8 (25)
Hypertension related events by prior kidney transplant			
Prior kidney transplant	2/7 (29)	1/8 (13)	3/15 (20)
No prior kidney transplant	6/10 (60)	4 /12 (33)	10 /22 (45)
Hypertension- related events by Baseline eGFR (mL/min/1.73 m^2)			
<15	4/7 (57)	1 /4 (25)	5 /11 (45)
15-<30	2/5 (40)	2/6 (33)	4/11 (36)
30- <60	2/5 (40)	2/8 (25)	4 /13 (31)
≥60	0/0	0 /2	0 /2

Source: Primary Tables of Safety Analyses in Module 5.3.5.3

Adverse events of hypertension occurred at any time during the eculizumab treatment period with a median of 112 days. These events occurred as early as the first dose and as late as 252 days. In nearly half of the patients, the event of hypertension occurred on the day of the infusion but in some patients was reported as late as 28 days post infusion. Despite the temporal relationship with eculizumab administration, in most cases, these events were not considered drug-related.

Laboratory findings

Laboratory assessments were performed on the data pooled across both prospective controlled studies including all 37 patients. A total of 27 patients had normal white blood cell (WBC) counts while 9 patients had leukopenia at baseline (Table 71). Twenty of the 27 patients with WBC counts in the normal range at baseline developed leukopenia during the course of the studies. In five of these 20 patients, leukopenia was related to the use of immunosuppressive agents to prevent graft rejection in transplanted patients. In the remaining 15 patients, leukopenia was transient and of short duration. Lymphocytopenia was transient and neutropenia was also transient and occurred in only a few patients with normal baseline value.

Table 71: Hematology (Studies C08-002A/B and C08-003A/B)

		Worst value during treatment No (%) of patients			
Lab Test Name	Baseline	Total	Low	Normal	High
WBC					
	Low	9	9 (100)	0	0
	Normal	27	19 (704)	8 (30)	0
	High	1	0	1 (100)	0
Lymphocytes					
	Low	19	19 (100)	0	0
	Normal	15	14 (93)	1 (3)	0
	High	2	0	2 (100)	0
Neutrophils					
	Low	1	1(100)	0	0
	Normal	25	4 (16)	21 (84)	0
	High	10	1 (10)	8 (80)	1 (10)

Source: Primary Tables of Safety Summary in Module 5.3.5.3

Hepatic findings

The vast majority of patients had normal liver enzymes at baseline (Table 72). Among patients with normal baseline values, none worsened during eculizumab treatment. Three out of 4 patients with elevated alanine transaminase (ALT) and aspartate aminotransferase (AST) at baseline normalised those enzymes during treatment. Five of the 35 patients with normal albumin at baseline had a single reading of low albumin during the study which returned into the normal range at the subsequent measurement. Fourteen of the 27 patients with normal protein at baseline experienced a low value during study period. In four of these fourteen patients the low value was a result of a single measurement and transient changes were observed in the remaining 10 patients. In all patients, total protein returned to normal and remained in the normal range. Also, albumin levels did not appear to change measurably.

Table 72: Liver Function Tests (Studies C08-002A/B and C08-003A/B)

			Worst value during treatment No (%) of patients		
Lab Test Name	**Baseline**	**Total**	**Low**	**Normal**	**High**
ALT					
	Low	0	0	0	0
	Normal	33	0	33 (100)	0
	High	4	0	3 (75)	1 (25)
AST					
	Low	0	0	0	0
	Normal	33	0	33 (100)	0
	High	4	0	3 (75)	1 (25)
Alkaline Phosphatase					
	Low	0	0	0	0
	Normal	36	6 (17)	30 (83)	0
	High	1	0	0	1 (100)
Bilirubin, Total					
	Low	7	7 (100)	0	0
	Normal	30	19 (63)	11 (37)	0
	High	0	0	0	0
Albumin					
	Low	2	2 (100)	0	0
	Normal	35	5 (14)	30 (86)	0
	High	0	0	0	0
Total Protein					
	Low	10	10 (100)	0	0
	Normal	27	14 (52)	13 (48)	0
	High	0	0	0	0

Source: Tables of Safety Summary in Module 5.3.5.3

Other serum chemistries

A total of 32 patients had elevated blood urea nitrogen (BUN) at baseline which normalized in 11 reflecting improvement in renal function. Twenty-one patients had normal uric acid at baseline and one patient's uric acid minimally worsened during treatment. One patient developed a transient elevation of serum glucose which promptly returned to normal value and remained in the normal range for the duration of the treatment period.

Electrolytes

Electrolyte abnormalities were observed (Table 73). These abnormalities were usually minimal and mostly transient in nature.

Table 73: Electrolytes (Studies C08-002A/B and C08-003A/B)

			Worst value during treatment No (%) of patients		
Lab Test Name	Baseline	Total	Low	Normal	High
Bicarbonate					
	Low	15	15 (100)	0	0
	Normal	20	18 (90)	2 (10)	0
	High	2	1 (50)	1 (50)	0
Chloride					
	Low	1	1 (100)	0	0
	Normal	35	9 (26)	26 (74)	0
	High	1	0	1 (100)	0
Sodium					
	Low	2	2 (100)	0	0
	Normal	35	10 (29)	25 (71)	0
	High	0	0	0	0

Source: Primary Tables of Safety Summary in Module 5.3.5.3

Safety in Special Groups and Situations

Subgroup analyses of AEs and SAEs as a function of intrinsic factors (age, sex, race, and geographic location) and extrinsic factors (prior kidney transplant, presence or absence of complement factor mutation, and baseline renal function expressed as eGFR) were conducted for studies C08-002A/B and C08-003A/B

- Age

The majority of patients enrolled in studies C08-002A/B and C08-003A/B were between 18 and 45 years of age, and six patients were adolescents. Due to the limited number of patients enrolled in the < 18 and >45 years age groups, no clinically meaningful comparisons for these studies can be made based on age.

In the retrospective study certain adverse events were noted to be more prevalent in the paediatric population than in the adult population. Tachycardia was noted in 27% of paediatric patients and no adult patients. Likewise, pyrexia was reported in 53% of paediatric patients and no adult patients. Thirty three percent of paediatric patients also reported upper respiratory tract infections compared with 9% of adults. Other AEs were reported with similar frequencies in both populations.

Table 74: Adverse Events by Age Groups (Study C09-001r)

	N (%) of Patients		
	Pediatric	**Adolescent**	**Adult**
	N=15	**N=4**	**N=11**
PATIENTS WITH AT LEAST 1 ADVERSE EVENT	10 (67)	4 (100)	8 (73)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (13)	1 (25)	3 (27)
Anemia	2 (13)	0	1 (9)
CARDIAC DISORDERS	5 (33)	0	1 (9)
Tachycardia	4 (27)	0	0
EYE DISORDERS	4 (27)	0	1 (9)
GASTROINTESTINAL DISORDERS	7 (47)	1 (25)	5 (45)
Abdominal pain	1 (7)	1 (25)	1 (9)
Diarrhea	5 (33)	1 (25)	2 (18)
Nausea	1 (7)	0	2 (18)
Vomiting	3 (20)	1 (25)	3 (27)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (53)	1 (25)	3 (27)
Pyrexia	8 (53)	1 (25)	0
INFECTIONS AND INFESTATIONS	10 (67)	1 (25)	7 (64)
Influenza	2 (13)	0	1 (9)
Nasopharyngitis	1 (7)	1 (25)	1 (9)
Upper respiratory tract infection	5 (33)	0	1 (9)
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS	2 (13)	1 (25)	0
INVESTIGATIONS	4 (27)	0	3 (27)
METABOLISM AND NUTRITION DISORDERS	4 (27)	2 (50)	2 (18)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (13)	2 (50)	2 (18)
NERVOUS SYSTEM DISORDERS	6 (40)	1 (25)	4 (36)
Headache	2 (13)	0	3 (27)
PSYCHIATRIC DISORDERS	3 (2)	1 (25)	3 (27)
Insomnia	0	1 (25)	2 (18)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8 (53)	0	3 (27)
Cough	5 (33)	0	2 (18)
Nasal Congestion	4 (27)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (20)	1 (25)	3 (27)

	N (%) of Patients		
	Pediatric	**Adolescent**	**Adult**
	N=15	**N=4**	**N=11**
VASCULAR DISORDERS	1 (7)	1 (25)0	1 (9)
Hypertension	1 (7)	0	1 (9)

Source Primary Tables of Safety Summary in Module 5.3.5.3

- Sex

Overall, there were no major differences in the incidence of AEs, SAEs and drug-related AEs based on sex.

- Race

Based on the limited number of patients enrolled in other race categories, no clinically meaningful comparisons can be made based on race for AEs, SAEs and drug-related AEs

- Geographic Region

There were no differences in AE reporting between the two subgroups. There were a higher proportion of patients who had an SAE among North American patients mostly related to the rate of hypertension-related SAEs

- Kidney Transplant Status

Approximately 41% of patients enrolled in studies C08-002A/B and C08-003A/B were prior recipients of a kidney transplant. Overall, there were no major differences in the incidence of AEs based on transplant status. Adverse events related to blood and lymphatic system disorders were more frequent in transplanted patients. Specifically lymphopenia and leukopenia were reported only in transplanted patients reflecting the use of immunosuppressive agents in this patient population. As discussed previously, hypertensive events were somewhat lower in transplanted patients than non-transplanted patients, however, there were no major differences in terms of drug-related AEs and SAEs.

- Presence of Mutations in Complement Regulatory Factors (CRF) or Auto Antibody to CRF(s)

Overall, there were no major differences in the incidence of AEs between patients with or without an identified complement regulatory factor genetic mutation or autoantibodies against complement regulatory factor proteins.

- Baseline Renal Function

Overall, there was no evidence of any differences in the rate of adverse events between the various subgroups based on baseline eGFR. The rate of SAE reporting was however higher in patients with a baseline eGFR <15 mL/min/1.73m2 and to a lesser extent among those with a baseline eGFR 15-<29 mL/min/1.73m2 which was mostly related to the reporting of hypertension events.

- Drug Interactions

Drug interactions were not studied in C08-002A/B, C08-003A/B or C09-001r.

HAHA Results

No neutralizing HAHA responses were observed in any of the 37 aHUS patients treated with eculizumab in the C08-002A/B and C08-003A/B studies, some of whom have been treated for up to 64 weeks. Consequently, there has been no apparent impact of HAHA on the PK/PD parameters evaluated for eculizumab. There was no detectable HAHA response in the 20 patients in the C08-003A/B study. Of

the 17 patients in the C08-002A/B study, one patient showed evidence of a HAHA response in both the screening assay and the confirmatory assay. This patient received one dose of eculizumab and discontinued from the study due to a diagnosis of systemic lupus erythematosus. There was no evidence of neutralization or intolerance in this patient as confirmed by the Neutralizing Anti-Drug Antibodies Assay Method (BTM-0047). Although the presence of antibodies has not been detected yet, it cannot be fully excluded. The MAH is initiating a study (reflected in the RMP) to collect data on the development of HAHA associated with long-term use of eculizumab (M07-003).

Update of safety data.

Further to the CHMP request, the applicant has provided data on long-term safety in the target population for the two prospective studies C08-002A/B and C08-003A/B. No update was obtained in the retrospective study (C09-001r) as data could only be collected up to the date of signature on the informed consent form. All safety data were collected up to March 15, 2011 corresponding to a median follow-up of 64 and 62 weeks respectively in study C08-002A/B and C08-003A/B. Overall, 28 (76%) of the 37 patients included in the two prospective studies had a minimum follow-up of 1 year.

Despite the increase in follow-up period, the overall safety profile remains similar in each prospective study and in the pooled analysis of safety. There were very limited differences between the original submission and the current update (Table 75). The most notable change was the increase in the total number of reported serious adverse events (SAEs) which were mostly attributed to study C08-003A/B, despite that, PT sensitive patients showed lower rates of drug-related AEs, severe AEs, SAE and drug-related SAEs compared to PT-resistant AHUS patients. All patients experienced at least one adverse event. Most adverse events were not drug-related and only 3 patients experienced a severe drug-related event.

Table 75: Overview of Adverse events (studies C08-002A/B and C08-003A/B)

	No (%) of patients					
	C08-002A/B (N= 17)		C08-003A/B (N= 20)		Total (N= 37)	
	Submission	Update	Submission	Update	Submission	Update
Patients with any AE	17 (100)	17 (100)	19 (95)	20 (100)	36 (97)	37 (100)
Patients with any drug-related AE	10 (59)	12 (71)	6 (30)	7 (35)	16 (43)	19 (51)
Patients with any severe AE	8 (47)	10 (59)	4 (20)	6 (30)	12 (32)	16 (43)
Patients with any severe drug-related AE	1 (6)	1 (6)	2 (10)	2 (10)	3 (8)	3 (8)
Patients with any SAE	15 (88)	17 (100)	5 (25)	10 (50)	20 (54)	27 (73)
Patients with any drug-related SAE	3 (18)	4 (24)	2 (10)	2 (10)	5 (14)	6 (16)
Patients with adverse events leading to discontinuation	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Patients with any drug-related adverse event leading to discontinuation	0	0	0	0	0	0

Adverse events were generally similar in the original submission and the current update (Table 76). The most notable difference was the increased reporting of hypertension and infections, which were observed in both studies. Hypertension increased from four (24%) to eight (47%) in study C08-002A/B and from 5 (25%) to 7 (35%) in study C08-003A/B. Infectious increased from 65% to 82% in PT-

resistant and from 65% to 85% in PT-sensitive patients. Both are risks are mentioned in the SPC and will be closely followed up in the postmarketing. Nausea, vomiting, hypotension, headache and nasopharyngitis were the only AEs for which an increase by four patients or more were noted. All other changes were minimal (≤ 3 patients) and consistent with what would be expected with additional follow-up in patients with a severe chronic disease. Diarrhea, upper respiratory infection, sinusitis, gastroenteritis, fatigue and asthenia were reported by three additional patients. The change in the number of patients reporting other AEs was ≤ 2 patients between submission and the safety update. Of note, one patient reported pharyngolaryngeal pain in the initial submission. In the update, this event was reclassified as upper respiratory tract infection by the investigator.

Thirteen AEs were reported by >10% of patients at the update but reported by ≤ 10% of patients at submission and include: asthenia, gastroenteritis, sinusitis, hypotension, pain, hypersensitivity, bronchitis, herpes zoster, muscles spasms, dizziness, epistaxis, rhinorrhea and rash.

Table 76: All adverse events reported in > 10% of patients (studies C08-002A/B and C08-003A/B)

Body System Adverse Event (Preferred Term)	No (%) of patients					
	C08-002A/B N= 17		C08-003A/B N= 20		Total N= 37	
	Submission	Update	Submission	Update	Submission	Update
Subjects with at least 1 AE	17 (100)	17 (100)	19 (95)	20 (100)	36 (97)	37 (100)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	10 (59)	10 (59)	7 (35)	10 (50)	17 (46)	20 (54)
Anaemia	6 (35)	6 (35)	3 (15)	4 (20)	9 (24)	10 (27)
Leukopenia	4 (24)	4 (24)	2 (10)	3 (15)	6 (16)	7 (19)
CARDIAC DISORDERS	2 (12)	3 (18)	0	1 (5)	2 (5)	4 (11)
EAR AND LABYRINTH DISORDERS	1 (6)	1 (6)	3 (15)	6 (30)	4 (11)	7 (19)
Vertigo	1 (6)	1 (6)	3 (15)	3 (15)	4 (11)	4 (11)
EYE DISORDERS	2 (12)	5 (29)	1 (5)	2 (10)	3 (8)	7 (19)
GASTROINTESTINAL DISORDERS	12 (71)	14 (82)	15 (75)	15 (75)	27 (73)	29 (78)
Abdominal pain	0	0	4 (20)	4 (20)	4 (11)	4 (11)
Diarrhoea	6 (35)	7 (41)	6 (30)	8 (40)	12 (32)	15 (41)
Nausea	4 (24)	5 (29)	3 (15)	7 (35)	7 (19)	12 (32)
RENAL AND URINARY DISORDERS	7 (41)	9 (53)	4 (20)	6 (30)	11 (30)	15 (41)
Renal impairment	4 (24)	4 (24)	2 (10)	2 (10)	6 (16)	6 (16)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (12)	3 (18)	0	1 (5)	2 (5)	4 (11)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (35)	7 (41)	5 (25)	8 (40)	11 (30)	15 (41)
Cough	2 (12)	3 (18)	3 (15)	4 (20)	5 (14)	7 (19)
Epistaxis	2 (12)	2 (12)	1 (5)	2 (10)	3 (8)	4 (11)
Pharyngolaryngeal pain	1 (6)	1 (6)	4 (20)	3 (15)	5 (14)	4 (11)
Rhinorrhoea	1 (6)	1 (6)	1 (5)	3 (15)	2 (5)	4 (11)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (24)	7 (41)	3 (15)	5 (25)	7 (19)	12 (32)
Rash	2 (12)	2 (12)	0	2 (10)	2 (5)	4 (11)
VASCULAR DISORDERS	9 (53)	13 (77)	6 (30)	9 (45)	15 (41)	22 (60)
Hypertension	4 (24)	8 (47)	5 (25)	7 (35)	9 (24)	15 (41)
Hypotension	0	2 (12)	1 (5)	3 (15)	1 (3)	5 (14)

Vomiting	5 (29)	6 (35)	3 (15)	6 (30)	8 (22)	12 (32)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10 (59)	14 (82)	9 (45)	14 (70)	19 (51)	28 (76)
Asthenia	1 (6)	3 (18)	2 (10)	3 (15)	3 (8)	6 (16)
Fatigue	3 (18)	3 (18)	1 (5)	4 (20)	4 (11)	7 (19)
Oedema peripheral	3 (18)	5 (29)	1 (5)	1 (5)	4 (11)	6 (16)
Pain	1 (6)	3 (18)	1 (5)	1 (5)	2 (5)	4 (11)
Pyrexia	3 (18)	4 (24)	1 (5)	4 (20)	4 (11)	8 (22)
IMMUNE SYSTEM DISORDERS	1 (6)	3 (18)	5 (25)	5 (25)	6 (16)	8 (22)
Hypersensitivity	0	1 (6)	3 (15)	3 (15)	3 (8)	4 (11)
INFECTIONS AND INFESTATIONS	11 (65)	14 (82)	13 (65)	17 (85)	24 (65)	31 (84)
Bronchitis	1 (6)	3 (18)	0	1 (5)	1 (3)	4 (11)
Gastroenteritis	1 (6)	3 (18)	1 (5)	2 (10)	2 (5)	5 (14)
Herpes zoster	2 (12)	2 (12)	0	2 (10)	2 (5)	4 (11)
Nasopharyngitis	1 (6)	2 (12)	7 (35)	10 (50)	8 (22)	12 (32)
Sinusitis	1 (6)	2 (12)	1 (5)	3 (15)	2 (5)	5 (14)
Upper respiratory tract infection	4 (24)	4 (24)	3 (15)	6 (30)	7 (19)	10 (27)
Urinary tract infection	4 (24)	5 (29)	2 (10)	2 (10)	6 (16)	7 (19)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (24)	5 (29)	2 (10)	5 (25)	6 (16)	10 (27)
INVESTIGATIONS	3 (18)	4 (24)	3 (15)	6 (30)	6 (16)	10 (27)
METABOLISM AND NUTRITION DISORDERS	8 (47)	11 (65)	3 (15)	6 (30)	11(30)	17 (46)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	10 (59)	11 (65)	5 (25)	9 (45)	15 (41)	20 (54)
Muscle spasms	2 (12)	2 (12)	1 (5)	2 (10)	3 (8)	4 (11)
Pain in extremity	1 (6)	1 (6)	3 (15)	3 (15)	4 (11)	4 (11)
NERVOUS SYSTEM DISORDERS	11 (65)	11 (65)	4 (20)	9 (45)	15 (41)	20 (54)
Dizziness	3 (18)	3 (18)	0	1 (5)	3 (8)	4 (11)
Headache	7 (41)	7 (41)	4 (20)	8 (40)	11 (30)	15 (41)
PSYCHIATRIC DISORDERS	6 (35)	7 (41)	1 (5)	3 (15)	7 (19)	10 (27)
Insomnia	4 (24)	4 (24)	1 (5)	2 (10)	5 (14)	6 (16)

A total of 16 (43%) patients (10 in study C08-002A/B and 6 in study C08-003A/B) had at least one severe AE at the safety update compared to 12 (32%) at submission (Table 77). Two patients in each prospective study (C08-002A/B and C08-003A/B) accounted for this increase in the reporting of severe AEs.

Overall, each adverse event classified as severe occurred in one patient with the exception of hypertension and anaemia which was each reported by a total of two patients (5%).

Ten AEs were reported as severe at the update but not during submission. These AEs include pain reported by one patient in study C08-002A/B, and impaired gastric emptying, influenza, pneumonia, dialysis device complication, malnutrition, peripheral sensory neuropathy, depression, renal mass, and embolism venous each reported by one patient in study C08-003A/B. Of note, one patient (Patient 3-197-001) reported severe vomiting and severe diarrhoea) in the initial submission. In the update, this event was reclassified by the investigator as severe dialysis device complication.

Table 77: Severe adverse events, all causes (studies C08-002A/B and C08-003A/B)

Body System Adverse Event (Preferred Term)	No (%) of patients					
	C08-002A/B N= 17		C08-003A/B N= 20		Total N= 37	
	Submission	Update	Submission	Update	Submission	Update
Subjects with at least 1 AE	8 (47)	10 (59)	4 (20)	6 (30)	12 (32)	16 (43)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (6)	2 (12)	0	0	1 (3)	2 (5)
Anaemia	1 (6)	2 (12)	0	0	1 (3)	2 (5)
GASTROINTESTINAL DISORDERS	0	0	2 (10)	2 (10)	2 (5)	2 (5)
Diarrhoea	0	0	1 (5)	0	1 (3)	0
Impaired gastric emptying	0	0	0	1 (5)	0	1 (3)
Peritonitis	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Vomiting	0	0	1 (5)	0	1 (3)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (6)	2 (12)	0	0	1 (3)	2 (5)
Fatigue	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Pain	0	1 (6)	0	0	0	1 (3)
INFECTIONS AND INFESTATIONS	0	0	0	2 (10)	0	2 (5)
Influenza	0	0	0	1 (5)	0	1 (3)
Pneumonia	0	0	0	1 (5)	0	1 (3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	1 (5)	0	1 (3)
Dialysis device complication	0	0	0	1 (5)	0	1 (3)
HEPATOBILIARY DISORDERS	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Cholelithiasis	1 (6)	1 (6)	0	0	1 (3)	1 (3)
METABOLISM AND NUTRITION DISORDERS	0	0	0	1 (5)	0	1 (3)
Malnutrition	0	0	0	1 (5)	0	1 (3)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Systemic lupus erythematosus	1 (6)	1 (6)	0	0	1 (3)	1 (3)
NERVOUS SYSTEM DISORDERS	3 (18)	3 (18)	0	1 (5)	3 (8)	4 (11)
Convulsion	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Headache	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Reversible posterior leukoencephalopathy syndrome	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Peripheral sensory neuropathy	0	0	0	1 (5)	0	1 (3)
PSYCHIATRIC DISORDERS	0	0	0	1 (5)	0	1 (3)
Depression	0	0	0	1 (5)	0	1 (3)
RENAL AND URINARY DISORDERS	1 (6)	1 (6)	1 (5)	2 (10)	2 (5)	3 (8)
Renal failure, chronic	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Renal impairment	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Renal mass	0	0	0	1 (5)	0	1 (3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Epistaxis	0	0	1 (5)	1 (5)	1 (3)	1 (3)
VASCULAR DISORDERS	3 (18)	4 (24)	2 (10)	2 (10)	5 (14)	6 (16)
Embolism venous	0	1 (6)	0	0	0	1 (3)
Hypertension	2 (12)	2 (12)	0	0	2 (5)	2 (5)
Hypotension	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Malignant hypertension	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Vein disorder	0	0	1 (5)	1 (5)	1 (3)	1 (3)

At the update, adverse events considered related to the study drug were reported by a total of 19 (51%) patients compared to 16 (43%) at submission (Table 78). Drug-related AEs were generally mild to moderate in severity as only three patients reported four severe drug-related AEs. The most notable difference was for the number of patients who reported a possibly drug related infection (7 vs. 4). The infections which were considered possibly drug-related included asymptomatic bacteriuria (C08-002A/B) and influenza infection and nasopharyngitis (C08-003A/B). Drug-related AEs which were reported for the first time during this update included: fatigue, asymptomatic bacteriuria, influenza infection, nasopharyngitis, nasal congestion and hypotension.

Of note, one patient in study C08-003A/B reported vertigo in the initial submission that was judged by the Investigator to be drug related. The relationship of this event was reclassified by the Investigator as unrelated and is no longer included in this table.

Table 78: Drug-related adverse events reported in ≥5% of patients (studies C08-002A/B and C08-003A/B)

Body System Adverse Event (Preferred Term	Number (%) of Patients					
	C08-002A/B N= 17	C08-002A/B N= 17	C08-003A/B N= 20	C08-003A/B N= 20	Total N= 37	Total N= 37
	Submission	Update	Submission	Update	Submission	Update
Patients with at least 1 drug-related AE	10 (59)	12 (71)	6 (30)	7 (35)	16 (43)	19 (51)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (12)	2 (12)	3 (15)	3 (15)	5 (14)	5 (14)
Leukopenia	2 (12)	2 (12)	2 (10)	2 (10)	4 (11)	4 (11)
Lymphopenia	0	0	2 (10)	2 (10)	2 (5)	2 (5)
EAR AND LABYRINTH DISORDERS	1 (6)	1 (6)	1 (5)	0	2 (5)	1 (3)
Vertigo	1 (6)	1 (6)	1 (5)	0	2 (5)	1 (3)
GASTROINTESTINAL DISORDERS	2 (12)	2 (12)	1 (5)	1 (5)	3 (8)	3 (8)
Nausea	2 (12)	2 (12)	0	0	2 (5)	2 (5)
Vomiting	2 (12)	2 (12)	0	0	2 (5)	2 (5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (12)	3 (18)	1 (5)	1 (5)	3 (8)	4 (11)
INFECTIONS AND INFESTATIONS	3 (18)	4 (24)	1 (5)	3 (15)	4 (11)	7 (19)
INVESTIGATIONS	2 (12)	2 (12)	0	0	2 (5)	2 (5)
NERVOUS SYSTEM DISORDERS	2 (12)	2 (12)	2 (10)	2 (10)	4 (11)	4 (11)
Headache	1 (6)	1 (6)	2 (10)	2 (10)	3 (8)	3 (8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	1 (5)	2 (10)	1 (3)	2 (5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (12)	2 (12)	1 (5)	1 (5)	3 (8)	3 (8)
VASCULAR DISORDERS	3 (18)	3 (18)	1 (5)	2 (10)	4 (11)	5 (14)
Accelerated hypertension	2 (12)	2 (12)	0	0	2 (5)	2 (5)

Three patients (1 in study C08-002A/B and 2 in study C08-003A/B) reported a total of 4 severe and possibly drug-related adverse events (influenza, peritonitis, hypertension and vein disorder). The only difference compared to the original submission was one patient in study C08-003A/B who had a possibly drug-related episode of influenza which occurred on Day 406 of eculizumab treatment. This patient's influenza resolved within two months of onset with medical treatment.

In the current update, seven additional patients reported at least one SAE (Table 79). All patients in study C08-002A/B reported at least one SAE while only half of patients in study C08-003A/B reported an SAE.

The largest number of patients reporting SAEs at the safety update was for infections. Five patients (all in study C08-003A/B) reported additional SAEs of infection. These infections included influenza (one

patient), pneumonia (one patient), norovirus (one patient), chronic hepatitis E (one patient) and Q fever (one patient). All infections with the exception of influenza were considered by the investigator to be unrelated to study drug. Of note, the patient with chronic hepatitis E had a history of hepatitis E infection and the patient with Q fever had their immune system compromised after renal transplant. Other additional SAEs reported during the extended follow-up included: pericardial effusion, transplant rejection, venous embolism and venous thrombosis.

Table 79: All serious adverse events reported by patients (studies C08-002A/B and C08-003A/B)

Body system Adverse Event	No. (%) of patients					
	C08-002 (N= 17)		C08-003 (N= 20)		Total (N= 37)	
	Submission	Update	Submission	Update	Submission	Update
Subjects with any Serious AE	15 (88)	17 (100)	5 (25)	10 (50)	20 (54)	27 (73)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (12)	4 (24)	0	0	2 (5)	4 (11)
Anemia	0	1 (6)	0	0	0	1 (3)
Hemolytic anemia	0	1 (6)	0	0	0	1 (3)
Leukopenia	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Pancytopenia	1 (6)	1 (6)	0	0	1 (3)	1 (3)
CARDIAC DISORDERS	2 (12)	2 (12)	0	1 (5)	2 (5)	3 (8)
Bradycardia	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Pericardial effusion	1 (6)	1 (6)	0	1 (5)	1 (3)	2 (5)
GASTROINTESTINAL DISORDERS	1 (6)	1 (6)	1 (5)	2 (10)	2 (5)	3 (8)
Impaired gastric emptying	0	0	0	1 (5)	0	1 (3)
Esophagitis	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Pancreatitis acute	0	1 (6)	0	0	0	1 (3)
Peritonitis	0	0	1 (5)	1 (5)	1 (3)	1(3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (6)	1 (6)	0	0	1 (3)	1 (3%)
Pyrexia	1 (6)	1 (6)	0	0	1 (3)	1 (3)
HEPATOBILIARY DISORDERS	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Cholelithiasis	1 (6)	1 (6)	0	0	1 (3)	1 (3)
IMMUNE SYSTEM DISORDERS	0	1 (6)	1 (5)	1 (5)	1 (3)	2 (5)
Transplant rejection	0	1 (6)	1 (5)	1 (5)	1 (3)	2 (5)
INFECTIONS AND INFESTATIONS	4 (24)	4 (24)	1 (5)	6 (30)	5 (14)	10 (27)
Asymptomatic bacteriuria	0	1 (6)	0	0	0	1 (3)
Bronchitis	0	1 (6)	0	0	0	1(3)
Clostridium difficile colitis	0	0	1 (5)	1 (5)	1 (3)	1 (3%)

Gastroenteritis	1 (6)	1 (6%)	0	0	1 (3)	1 (3)
Gastroenteritis norovirus	0	0	0	1 (5)	0	1 (3)
Hepatitis e	0	0	0	1 (5)	0	1 (3)
Influenza	0	0	0	1 (5)	0	1 (3)
Pneumonia	0	0	0	1 (5)	0	1 (3)
Q fever	0	0	0	1 (5)	0	1 (3)
Upper respiratory tract infection	2 (12)	2 (12)	0	0	2 (5)	2 (5)
Varicella	1 (6)	1 (6)	0	0	1 (3)	1 (3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (6)	1 (6)	0	1 (5)	1 (3)	2 (5)
Dialysis device complication	0	0	0	1 (5)	0	1 (3)
Respiratory fume inhalation disorder	1 (6)	1 (6)	0	0	1 (3)	1 (3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (12)	2 (12)	0	0	2 (5)	2 (5)
Back pain	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Systemic lupus erythematosus	1 (6)	1 (6)	0	0	1 (3)	1 (3)
NERVOUS SYSTEM DISORDERS	2 (12)	3 (18)	1 (5)	1 (5)	3 (8)	4 (11)
Convulsion	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Headache	0	1 (6)	1 (5)	1 (5)	1 (3)	2 (5)
Reversible posterior leukoencephalopathy syndrome	1 (6)	1 (6)	0	0	1 (3)	1 (3)
PSYCHIATRIC DISORDERS	0	1 (6)	0	0	0	1 (3)
Alcohol withdrawal syndrome	0	1 (6)	0	0	0	1 (3)
RENAL AND URINARY DISORDERS	4 (24)	4 (24)	1 (5)	2 (10)	5 (14)	6 (16)
Hematuria	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Renal failure acute	0	1 (6)	0	0	0	1 (3)
Renal failure chronic	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Renal impairment	3 (18)	3 (18)	0	0	3 (8)	3 (8)
Renal mass	0	0	0	1 (5)	0	1 (3)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (6)	1 (6)	0	0	1 (3)	1 (3)
Dyspnea	1 (6)	1 (6)	0	0	1 (3)	1 (3)
SURGICAL AND MEDICAL PROCEDURES	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Catheter removal	0	0	1 (5)	1 (5)	1 (3)	1 (3)
VASCULAR DISORDERS	6 (35)	7 (41)	2 (10)	3 (15)	8 (22)	10 (27)
Accelerated hypertension	2 (12)	2 (12)	0	0	2 (5)	2 (5)
Embolism venous	0	1 (6)	0	0	0	1 (3)
Hypertension	2 (12)	3 (18)	0	0	2 (5)	3 (8)
Hypotension	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Malignant hypertension	2 (12)	2 (12)	0	0	2 (5)	2 (5)
Vein disorder	0	0	1 (5)	1 (5)	1 (3)	1 (3)
Venous thrombosis limb	0	0	0	1 (5)	0	1 (3)

Other safety concerns

During the additional follow-up, there were no deaths and no AEs leading to discontinuation. During the additional follow-up, there was no report of any meningococcal infections in aHUS patients treated in the two prospective studies or in patients included in the retrospective trial.

Additional safety information

Studies C08-002A/B and studies C08-003A/B are currently on-going. Additional safety updates on those patients will be provided at the time of the conclusion of this study (target 2012). In addition, Alexion will implement a long-term follow-up study for all patients who were included in all aHUS studies (prospective and retrospective). This protocol is targeted to be implemented after the approval of the aHUS indication by competent authorities. This protocol will continue to collect additional safety information on targeted safety concerns including meningococcal infections, serious infections and severe clinical TMA complications of aHUS after discontinuation of eculizumab.

Post marketing experience

The cumulative post-marketing exposure is estimated to be approximately 2030 patient years. During 6 months preceding this report approximately 1232 patients (vast majority PNH patients) were treated with Soliris. A total of 828 AEs possibly related to Soliris were reported and 292 of these 898 AEs were medically confirmed. The majority of these AEs were previously reported in PNH clinical trials.

3.3.4.1. Discussion on Clinical Safety

The aHUS database is very limited, but so far, the AEs associated to the use of eculizumab are not different from the ones observed for PNH. Interestingly, though the presence of antibodies to Eculizumab has not been detected yet, although it cannot be fully excluded. In this regard, the Applicant is requested to include in their periodic safety update reports, a special section about the presence of antibodies to Eculizumab.

Nearly all patients experienced a treatment emergent adverse event. Generally speaking, the safety profile in both PNH and aHUS indications is similar. There have been some AEs frequently described in aHUS indication (hypertension, insomnia and vascular disorders) that were not described with the

same frequency in the PNH patients. Of note, the incidence of leucopoenia in 16% of patients is remarkable and although a relationship to eculizumab cannot be fully ruled out, the leucopoenia seems to be related to immunosuppressant agents. In any case, this AE is currently reflected in SmPC and will be closely monitored post-approval.

Importantly, there is a clearly different safety profile between the two populations studied, being worst for the PT resistant setting.

Serious AEs were reported in 20 (54%) patients treated in studies C08-002A/B and C08-003A/B. The most expected SAEs are those related to the immune systems. There were five SAEs of infection consisting of upper respiratory infections (two patients), varicella infection (one patient), gastroenteritis (one patient) and *Clostridium difficile* diarrhea (one patient). Regarding renal and urinary disorders as SAEs, the course of the disease likely has had an important contribution.

There were 3 SAEs related to central nervous system disorders. One patient had a seizure, one patient had reversible posterior leucoencephalopahy syndrome and one had a headache. Seizure and reversible posterior leucoencephalopathy were attributed to underlying hypertension. All patients recovered.

The four drug-related SAEs consisted of accelerated hypertension, hypertension and peritonitis.

Again there was a different profile in regards to the SAES depending on what type of population was treated, being worst for the PT resistant setting.

Two patients had cardiac disorders considered as serious. These two subjects represent 12% of the patients treated in the study C08-002 (both of them were in that study). Specifically, the SAEs were defined as bradycardia and pericardial effusion. The investigators did not judge these events as related to the study medication. The patient who underwent the pericardial effusion was considered as recovered with sequelae. Another patient with bradycardia was considered recovered.

The discontinuation of the treatment appears to induce a worsening of the disease, in many cases from an improved situation. This has been reflected in the SmPC (see section 4.4).

A total of 38 AEs related to infections other than due to Neisseria meningitidis were reported in 21 aHUS patients in the prospective clinical studies. Five infection events were considered as serious AEs. One additional event, gram positive peritonitis, also was reported, and was deemed serious due to hospitalization.

AEs of special interest not previously noted, hypertension and leukopenia were a new drug-related AE and the most commonly reported study drug-related AE, respectively.

Unfortunately, due to the limited sample size, it is not possible to obtain any reliable conclusions about different safety profile in specific subset of patients, although there seem to be some differences according to the age. The following adverse events were noted to be more prevalent in the paediatric than in the adult population: Tachycardia (27% vs 0%), eye disorders (27% vs 9%), Diarrhea (33% vs 18%) and Pyrexia (53% vs 0%).

The overall prevalence of infection in paediatric patients was 67% (N =10/15 patients) which was also similar to that observed in the adult patient group studied in the prospective studies (65%, N=24/37 patients)

The frequency of the most commonly reported AEs appears to increase in the long term, particularly in the PT-sensitive population, although it is noted that the majority of AEs described in the updated report are non serious, and of easy management in the clinical practice. The relationship with eculizumab is difficult to be established, as no direct comparison exists. Some of the AEs are probably

influenced by other baseline medicinal products, i.e. infections and infections by immunosuppressant. On the contrary, other AEs could be attributed to the experimental drug. In this regard, it should be noted the increase in diarrhoea, nausea, vomiting, fatigue, headache, hypertension, and infections might increase over time.

The overall safety profile appears acceptable and manageable in clinical practice. However, the limited database makes necessary a continuous follow-up and reassessment of the benefit/risk balance in the light of the available evidence and the better knowledge of eculizumab in the treatment of aHUS patients. In this respect, the MAH has agreed to perform a prospective long-term follow-up study (C11-003) which will include aHUS patients previously treated with eculizumab in the MAH clinical studies. In addition, a draft aHUS registry protocol (M11-001) has been included in the RMP and will collect and evaluate safety data specific to the use of eculizumab in aHUS as well as long-term effects.

In addition the MAH should submit half-yearly PSURs until otherwise agreed by the CHMP.

3.4. Summary of the EU RMP

An updated EU-RMP version 5.4 has been submitted to assess the new indication proposed by the company: Atypical Haemolytic Uremic Syndrome (aHUS).

The summary of the EU-RMP of the updated version submitted is as follows:

Safety Concern	Risk	Proposed Pharmacovigilance activities	Proposed Risk Minimization activities
Meningococcal infection	Identified	1. Routine Pharmacovigilance 2. PNH and aHUS Registries - Maintained at least 5 years - Includes collecting information for specific events 3. Events of Interest as part of additional Pharmacovigilance	**SmPC** Section 4.2 Posology and method of administration: Mandatory vaccination/re-vaccination against *Neisseria meningitidis* or prophylactic antibiotics Section 4.3 Contraindication: Patients with unresolved *Neisseria meningitidis* infection. Patients who are not currently vaccinated against *Neisseria meningitidis* or not receiving prophylactic antibiotics Section 4.4 Special warnings and precautions for use: Warning Meningococcal infection including fatalities. Section 4.8 Undesirable effects: Meningococcal sepsis listed as a common ADR and Neisseria infection listed as an uncommon ADR. **Package leaflet** Vigilance for risks of meningitis; need to be vaccinated. Early detection of symptoms of serious infection and steps to manage **Patient Safety Card** Warning for early detection of symptoms and advice to contact medical facility. To be shown to consulted physician for acknowledgement of the risk. **Physician's Guides to Prescribing** **Patients information brochures** **Controlled distribution system**
Sepsis	Identified	1. Routine Pharmacovigilance 2. PNH and aHUS Registries - Maintained at least 5 years - Includes collecting information for specific events 3. Events of Interest as part of additional Pharmacovigilance	**SmPC** Section 4.4 Special warnings and precautions for use : Other systemic infection. Section 4.8 Undesirable effects: Sepsis and Septic shock are identified as adverse drug reaction of common incidence.

			Package leaflet Vigilance for risks of infections. Early detection of symptoms of serious infection and steps to manage. **Patient Safety Card** Warning for early detection of symptoms and advice to contact medical facility. To be shown to consulted physician for acknowledgement of the risk. **Physician's Guide to Prescribing** **Patients information brochures**
Severe TMA complications due to discontinuation in aHUS patients	Identified	1. Routine Pharmacovigilance 2. aHUS Registry – Maintained at least 5 years – Includes collecting information for specific events 3. Events of Interest as part of additional Pharmacovigilance	**SmPC** • Section 4.4 Special warnings and precautions for use : Treatment Discontinuation and Laboratory Monitoring sections in section 4.4 **Package leaflet** • Vigilance for risks of discontinuation Need to carefully monitor for signs and symptoms of severe TMA following drug discontinuation **-Physician's Guide to Prescribing** **aHUS Patient/Parent information brochure**

Serious infections	Potential	1. Routine Pharmacovigilance 2. PNH and aHUS Registries - Maintained at least 5 years - Includes collecting information for specific events 3. Events of Interest as part of additional Pharmacovigilance	**SmPC** Section 4.4 Special warnings and precautions for use: Mentioned as adverse events in section 4.8. Mandatory vaccination against haemophilus and pneumococcus in children below 18 years of age according to national vaccination guidelines. Section 4.8 Undesirable effects: Type and incidence of infections are listed under the SOC "infection and infestations" **Package leaflet** Vigilance for risks of infections. Early detection of symptoms of serious infection and steps to manage. **Patient Safety Card** Warning for early detection of symptoms and advice to contact medical facility. To be shown to consulted physician for acknowledgement of the risk. **Physician's Guide to Prescribing** **Patients information brochures**
Infusion reactions	Identified	1. Routine Pharmacovigilance 2. PNH and aHUS Registries - Maintained at least 5 years - Includes collecting information for specific events 3. Events of Interest as part of additional Pharmacovigilance	**SmPC** Warning in section 4.4. **Package leaflet** Sections 2 and 3. **Physician's Guide to Prescribing** **Patients information brochures**
Immunogenicity	Potential	1. Routine Pharmacovigilance 2. PNH and aHUS Registries - Maintained at least 5 years - Includes collecting information for specific events 3. Human Anti-Human Antibodies (HAHA) study M07-003 4. Events of Interest as part of additional Pharmacovigilance	**SmPC** Warning in section 4.8. **Package leaflet** Sections 2. **Physician's Guide to Prescribing**
Serious haemolysis after drug discontinuation in	Potential	Routine Pharmacovigilance	**SmPC**

PNH patients		PNH Registry - Maintained at least 5 years - Includes collecting information for specific events Events of Interest as part of additional Pharmacovigilance	Warning: Treatment Discontinuation and Laboratory Monitoring sections in section 4.4 Package Leaflet Vigilance for risks of discontinuation Need to carefully monitor for signs and symptoms of serious haemolysis following drug discontinuation- Physician's Guide to Prescribing for patients with PNH PNH Patient information brochure
Malignancies Hematologic abnormalities in PNH	Potential	1. Routine Pharmacovigilance 2. PNH Registry - Maintained at least 5 years - Includes collecting information for specific events 3. Events of Interest as part of additional Pharmacovigilance	**SmPC** Section 4.8: Blood and lymphatic system disorders as well as malignant neoplasms adverse reactions are listed in table 1. This risk does not require further mitigation activities.
Pregnancy and lactation	Missing information	1. Routine Pharmacovigilance 2. PNH and aHUS Registries - Maintained at least 5 years - Includes collecting information for specific events 3. Events of Interest as part of additional Pharmacovigilance	**SmPC** Section 4.6 Fertility, Pregnancy and lactation: - Reflects lack of information. - "Soliris should be given only if clearly needed". - Recommendation of contraception for child bearing potential women. - Breast-feeding should be discontinued. **Package leaflet** In section 2 are mentioned recommendation of contraception methods. Need of contraception methods use. **Physician's Guide to Prescribing** **aHUS Patient/Parent information brochures and PNH Patient information brochure**
Children	Missing information	1. Routine Pharmacovigilance 2. PNH and aHUS Registries 3. Pediatric clinical studies M07-005 in PNH C10-003 in aHUS	**SmPC** The lack of experience in PNH children and adolescent is mentioned in Sections 4.2 and 5.2. Specific considerations regarding aHUS pediatric population are detailed in sections

			4.2, 4.4 and 5.2 **Physician's Guide to Prescribing** aHUS Patient/parent information brochure aHUS Parent information brochure
Patients with renal impairment	Missing information	1. Routine Pharmacovigilance 2. PNH and aHUS Registries 3. Event of Interest as part of additional Pharmacovigilance	**SmPC** Information is reflected in Sections 4.2 and 5.2. **Physician's Guide to Prescribing** aHUS Patient/Parent information brochure PNH Patient information brochure
Patients with hepatic impairment	Missing information	1. Routine Pharmacovigilance 2. PNH and aHUS registries pre-specified checklist 3. Events of Interest as part of additional Pharmacovigilance	**SmPC** Lack of information reflected in Sections 4.2 and 5.2. **Physician's Guide to Prescribing** aHUS Patient/Parent information brochure PNH Patient information brochure
Long term safety in aHUS patients	Missing information	1. Routine Pharmacovigilance 2. aHUS Registry 3. Clinical studies in aHUS C10-004 C11-003	None

The CHMP, having considered the data submitted in the application, is of the opinion that the amended risk minimisation activities as described in the conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II) and those to be addressed to the member states (Annex 127a) are adequate for the proposed new indication.

3.5. Changes to the Product Information

The MAH proposed the following changes to the product information (PI), to which the CHMP agreed:

4.1 Therapeutic indication:

Soliris (eculizumab) is indicated for the treatment of patients with:

- Paroxysmal nocturnal haemoglobinuria (PNH).

  Evidence of clinical benefit of Soliris in the treatment of patients with PNH is limited to patients with history of transfusions.

- Atypical hemolytic uremic syndrome (aHUS) (see section 5.1).

[...]

4.3 Contra-indications

[…]

Do not initiate Soliris therapy (see section 4.4) :

- in PNH patients:with unresolved *Neisseria meningitidis* infection.
- who are not currently vaccinated against *Neisseria meningitidis*
- ~~who have known or suspected hereditary complement deficiencies.~~

in aHUS patients:

- with unresolved *Neisseria meningitidis* infection.
- who are not currently vaccinated against *Neisseria meningitidis* or do not receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.

[…]

4.4 Special warnings and precautions for use

Meningococcal Infection:

[…]

Patients less than 2 years of age and those who are treated with Soliris less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination

[…]

Immunogenicity: Infrequent, low titre antibody responses have been detected in Soliris -treated patients across all ~~PNH and non-PNH~~ studies. In placebo controlled studies low titre responses have been reported with a frequency (3.4%) similar to that of placebo (4.8%).

[…]

Immunization: Prior to initiating Soliris therapy, it is recommended that PNH and aHUS patients should ~~receive~~initiate immunizations according to current immunization guidelines. Additionally, all patients must be vaccinated against meningococcus at least 2 weeks prior to receiving Soliris. Patients less than 2 years of age and those who are treated with Soliris less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. If available, tetravalent, conjugated vaccines are recommended (see meningococcal diseaseinfection).

Patients less than 18 years of age must be vaccinated against haemophilus influenzae and pneumococcal infections, and strictly need to adhere to the national vaccination recommendations for each age group.

[…]

aHUS Laboratory Monitoring

aHUS patients receiving Soliris therapy should be monitored for thrombotic microangiopathy by measuring platelet counts, serum LDH and serum creatinine, and may require dose adjustment within the recommended 14±2 day dosing schedule during the maintenance phase (up to every 12 days).

[…]Treatment Discontinuation for aHUS: Severe thrombotic microangiopathy complications were observed after Soliris discontinuation in the aHUS clinical studies. If aHUS patients discontinue

treatment with Soliris they should be monitored closely for signs and symptoms of severe thrombotic microangiopathy complications.

Severe thrombotic microangiopathy complications post discontinuation can be identified by (i) any two, or repeated measurement of any one, of the following: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during Soliris treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during Soliris treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during Soliris treatment; or (ii) any one of the following: a change in mental status or seizures; angina or dyspnoea; or thrombosis.

Monitor any patient who discontinues Soliris for at least 12 weeks to detect severe thrombotic microangiopathy complications.

If severe thrombotic microangiopathy complications occur after Soliris discontinuation, consider reinstitution of Soliris treatment, supportive care with PE/PI, or appropriate organ-specific supportive measures including renal support with dialysis, respiratory support with mechanical ventilation or anticoagulation. In aHUS clinical studies, 18 patients (5 in the prospective studies) discontinued Soliris treatment. Seven (7) severe thrombotic microangiopathy complications were observed following the missed dose in 5 patients and Soliris was re-initiated in 4 of these 5 patients.

Educational guidance

All physicians who intend to prescribe Soliris must ensure they are familiar with the physician's guide to prescribing. Physicians must discuss the benefits and risks of Soliris therapy with patients and provide them with a patient information brochure and a patient safety card.

Patients should be instructed that if they develop fever > 39°C, headache accompanied with fever and/or stiff neck or sensitivity to light, they should immediately seek medical care as these signs may be indicative of meningococcal infection.

Other changes to the PI have been introduced to sections 4.2, 4.8, 5.1, 5.2, 6.6 as highlighted in the annex 1 to the CHMP AR.

The PL has been updated accordingly. Furthermore the MAH took the opportunity of this variation to update the product information with the latest version of the QRD template.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3.6. Benefit-risk balance

Benefits

Beneficial effects

Treatment with Eculizumab in the PT-resistant population (Study C08-002A/B) improved or stabilised the kidney function, haematological parameters and systemic manifestation as measured by QoL. The results were robust and compelling in these patients without therapeutic alternatives, since these

patients were considered resistant to the usual treatment in aHUS (Plasma therapy). Overall, platelet counts increased and were within normal limits in 14 of 17 patients (82%; 95% CI: 57%-96%) during the eculizumab treatment period. The time to first occurrence of normal platelet count (≥ 150 x 10^9/L) occurred as early as one day following the first eculizumab dose, with a median time of 7 days to achieve a first occurrence of platelet count normalization. Regarding Haematologic Normalization, it was achieved by 76% of patients (95% CI:50-93%) and in up to 90% of the 10 patients with both abnormal platelet count and LDH at entry. Importantly, the duration of response continues into the extension phase, with a median duration of response limited only by the current data cut-off and is currently 258 days (range 196-431) for hematologic normalization and 267 days (range 217-389) for complete TMA response. Additionally, at the time of the data cut-off, 13 of the 17 patients in study C08-002A/B remained on treatment.

Results from the Study C08-003A/B, showed that a substantial majority of PT-sensitive patients receiving eculizumab in the study (16 of 20 patients [80%; 95% CI: 56- 94]) achieved the primary endpoint of TMA Event-Free Status through Week 26, which was sustained for a median time duration of approximately 40 weeks (280 days) as of the data cut-off date. Regarding Hematologic Normalization, it was achieved in almost all patients, demonstrating maintenance of normal platelet count after discontinuation of PT and start of eculizumab therapy. A total of 18 out of 20 patients (90%; 95% CI: 68-99) achieved Hematologic Normalization. 100% of study C08-003A/B patients who obtained hematologic normalization (and its components of platelet count normalization and LDH normalization) and complete TMA response indicating, that all patients who achieve an improvement in TMA, maintain that improvement with ongoing treatment. At the time of data cut-off, 19 of the 20 patients in study C08-003A/B also remain on eculizumab treatment.

Although no conclusion can be drawn on any potential benefit in renal function in the long-term, which is the ultimate goal of treatment, the available evidence support the use of eculizumab as an alternative to plasma therapy in the treatment of PT-sensitive population.

Efficacy in the paediatric population has been demonstrated throughout the evidence provided by the retrospective study C09-001 which included 30 patients. There were 15 paediatric patients and 4 adolescents. The efficacy of eculizumab as determined by measures of platelet count, TMA event free status, TMA intervention rate, haemoglobin and renal improvement was observed in all paediatric age groups from 2 months to 11 years. Almost all paediatric patients achieved or maintained a normal platelet count, including 6 of 7 patients who were thrombocytopenic (platelet count <150 × 10^9/L) before starting eculizumab. Similarly, 11/15 (73%) of paediatric patients achieved TMA event-free status with eculizumab treatment. TMA intervention rate significantly decreased from a median of 0.45 events per patient/day in the 28 days prior to eculizumab to 0 on eculizumab (P<0.0001). None of these patients required new dialysis. Clinically significant improvement in renal function was also noted in eight (53%) pediatric patients, and a clinically significant increase in hemoglobin (>20 g/L) was also observed in 53% of pediatric patients.

Regarding the update from the prospective studies C08-002A/B and C08-003A/B (until 64-63 weeks), it is worth highlighting that the efficacy of Soliris was maintained, or even improved, in the long term.

Risks

Unfavourable effects

Nearly all patients experienced a treatment emergent adverse event. Generally speaking, the safety profile in both PNH and aHUS indications is similar. The most frequently reported AEs in the aHUS indication were: diarrhea (32% of patients), vomiting (22%), nausea (19%) and abdominal pain

(11%), headache (30%), anemia (24%), Leukopenia (16%), hypertension (24%), infections and infestations (nasopharyngitis, upper respiratory tract and urinary tract infections), insomnia (14%) general disorders, administration site conditions, musculoskeletal and nervous system disorders (41%), vascular disorders (41%) and respiratory, thoracic and mediastinal disorders (30% of patients). There have been some AEs frequently described in aHUS indication (hypertension, insomnia and vascular disorders) that were not described with the same frequency in the PNH patients. However, in the CHMP's view the lack of control group precludes to determinate the actual frequency of these AEs and if they were related to the administration of Soliris or if the disease and concomitant therapy received might have contributed.

Serious AEs were reported in 20 (54%) patients treated in studies C08-002A/B and C08-003A/B. The most expected SAEs are those related to the immune systems. The four drug-related SAEs consisted of accelerated hypertension, hypertension and peritonitis.

The overall prevalence of infection in paediatric patients was 67% (N =10/15 patients) which was also similar to that observed in the adult patient group studied in the prospective studies (65%, N=24/37 patients). The following adverse events were noted to be more prevalent in the paediatric than in the adult population: tachycardia, eye disorders, diarrhoea and pyrexia.

The discontinuation of the treatment appears to induce a worsening of the disease, in many cases from an improved situation. This is considered as safety concern.

The frequency of the most commonly reported AEs appears to increase in the long term, particularly in the PT-sensitive population, although it is noted that the majority of AEs described in the updated report are non serious, and of easy management in the clinical practice. The relationship with eculizumab is difficult to be established, as no direct comparison exists. Some of the AEs are probably influenced by other baseline medicinal products, i.e. infections and infestations by immunosuppressant. On the contrary, other AEs could be attributed to the experimental drug. In this regard, it should be noted that AEs like diarrhoea, nausea, vomiting, fatigue, headache, hypertension, and infections might increase over time.

Balance

Importance of favourable and unfavourable effects

Treatment with Eculizumab in the PT-resistant population improved or stabilised the kidney function, haematologic parameters and systemic manifestation as measured by QoL. The results were robust and compelling in patients without therapeutic alternatives, since these patients were considered resistant to the usual treatment in aHUS (Plasma therapy). The clinical relevance of these outcomes has been convincingly demonstrated. The benefits clearly outweigh the known and potential risks of eculizumab that in general is well tolerated and the AEs profile of easy management in clinical practice.

In the PT-sensitive population eculizumab has demonstrated to be an effective alternative to plasma therapy. The benefit/risk balance is considered positive.

The evidence provided to support the indication in the paediatric population is limited and mainly based on retrospective data so far. However, the available results are consistent to those seen in the adult population, it is considered that these data are sufficient to establish a positive benefit-risk in the paediatric population. The limited database makes necessary a continuous follow-up and reassessment of the benefit/risk balance and therefore the PSUR cycle for the product will follow a yearly cycle until otherwise agreed by the CHMP.

Benefit-risk balance and Discussion on the benefit-risk assessment

The benefits showed by eculizumab in the treatment of aHUS (adults and children) outweigh the risk associated to this new therapy. The relatively high dose proposed in this indication raises some concerns and it is recommended to the MAH to further investigate the efficacy and safety of lower doses as post approval.

3.7. Recommendation

Based on the CHMP review of data on safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Soliris in the treatment of atypical haemolytic uremic syndrome (aHUS) was favourable and therefore recommended the granting of this extension of indication.

The PI has been brought in line with the latest QRD template version 8.0.

Conditions and requirements of the marketing authorisation

PSUR cycle

The PSUR cycle for the product will follow a half-yearly cycle until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The CHMP, having considered the data submitted in the application, is of the opinion that the amended risk minimisation activities as described in the conditions or restrictions with regard to the safe and effective use of the medicinal product (Annex II) and those to be addressed to the member states (Annex 127a) are adequate for the proposed new indication.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate the Package Leaflet.