21 March 2013
EMA/CHMP/126714/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Soliris

International non-proprietary name: ECULIZUMAB

Procedure No. EMEA/H/C/000791/II/0050

Note

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

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London, 21 March 2013
EMA/CHMP/126714/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Soliris

Procedure no. EMEA/H/C/000791/II/0050

Marketing authorisation holder (MAH): Alexion Europe SAS

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Alexion Europe SAS submitted to the European Medicines Agency on 6 December 2012 an application for a variation including an extension of indication

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Soliris	ECULIZUMAB	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC to include dose recommendations and additional information available in paediatric patients with PNH as requested by CHMP further to the assessment of ME2 14.2.

The Package Leaflet was proposed to be updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.3.

The variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Soliris was designated as an orphan medicinal product EU/3/03/166 on 17 October 2003. Soliris was designated as an orphan medicinal product in the following indication: Treatment of paroxysmal nocturnal haemoglobinuria.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/224/2010) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (Decision P/224/2010) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with

authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

Submission date:	6 December 2012
Start of procedure:	21 December 2012
Rapporteur's preliminary assessment report circulated on:	25 February 2013
PRAC RMP Rapporteur assessment adopted by PRAC	25 February 2013
Rapporteur's final assessment report circulated on	19 March 2013
CHMP opinion:	21 March 2013

2. Scientific discussion

2.1. Introduction

Eculizumab is a humanized monoclonal antibody (mAb) that binds with high affinity and selectivity to human complement protein C5, blocking its cleavage into the proinflammatory, prothrombotic C5a and lytic C5b-9 components, while leaving the upstream components of complement, most notably C3b, intact to preserve opsonization of pathogens and clearance of immune complexes.

Paroxysmal Nocturnal Hemoglobinuria (PNH) is a debilitating and life-threatening hematopoietic stem cell disorder characterized by uncontrolled activation of the complement system leading to chronic intravascular hemolysis and an inflammatory prothrombotic state. PNH evolves from the clonal expansion of hematopoietic stem cells with resulting in complete or marked loss of the glycosylphosphatidylinositol (GPI)-linked terminal complement inhibitors CD55 and CD59 from the surface of hematopoietic cells, rendering red blood cells susceptible to terminal complement-mediated hemolysis, and white blood cells and platelets susceptible to uncontrolled terminal complement-mediated activation.

A total of seven clinical studies (C02-001, E02-001, X03-001, C04-001 [TRIUMPH], C04-002 [SHEPHERD], E05-001 and C06-002) have been conducted by Alexion Pharmaceuticals, Inc. in adult PNH patients (i.e., 18 years and older) to assess the safety and efficacy of eculizumab therapy. These studies have confirmed that eculizumab was safe and well tolerated. Treatment with eculizumab modified the clinical course of PNH and was associated with significant reductions in thromboembolism, the leading cause of death in PNH, anemia, blood transfusions, and disease-related symptoms that included fatigue, pain and dyspnea, as well as improvements in patient functioning and global health status.

On 20 June 2007, the European Commission granted a marketing authorisation for Soliris (eculizumab) for the treatment of PNH based on the above mentioned studies in adult patients.

Since the granting of the marketing authorisation, the indication of Soliris has also been extended for the treatment of adult and paediatric patients with atypical haemolytic uraemic syndrome (aHUS).

At the time of the granting of the marketing authorisation, the Marketing authorisation Holder (MAH) committed to conduct a study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of eculizumab in paediatric patients with PNH.

The design of such a study was further discussed in the Paediatric Investigation Plan of Soliris (EMEA-000876-PIP01-10 approved on 10 September 2010). The MAH submitted the revised synopsis for Study M07-005 on 7 June 2010. This protocol was endorsed by the CHMP on 22 July 2010.

The final study report of Study M07-005 was submitted to the CHMP in March 2012 (FUM 014). Further to its assessment, the CHMP concluded on 21 June 2012 that the product information should be updated to include dose recommendations in paediatric patients.

This variation application has been submitted to that effect, with the MAH proposal to update sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC to include dose recommendations and additional information available in paediatric patients with PNH as requested by CHMP further to the assessment of ME2 14.2.

2.2. Quality aspects

The formulation, presentation and administration of eculizumab in study M07-005 were identical to those tested in the initial development plan and described in the approved SmPC. These have been previously described in the original PNH submission.

2.3. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

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.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of study	Study identifier	Indication	Study Objective (Phase) [1]	Study design and control [2]	Test product; Dosage Regimen [3]	Number of subjects		Healthy subjects / Diagnosis of Pts	Treatment duration	Study status, report type	Module 5 location
						Eculizumab	Placebo				
Clinical study in PNH	M07-005	PNH	PK, PD, Dose, S, E	ol	A	7	N/A	PNH	12 weeks	Complete; Full	5.3.5.2

2.4.2. Pharmacokinetics/Pharmacodynamics

Data in adults with PNH have shown that eculizumab concentrations greater than 35 µg/mL inhibited terminal complement formation and prevented intravascular hemolysis. Analyses of data in PNH clinical trials, however, demonstrated that terminal complement inhibition was incomplete in approximately

35% of patients after the first (induction) dose of eculizumab. In addition, in approximately 10 – 15% of PNH patients, terminal complement inhibition during the maintenance phase (Week 6) was not consistently sustained with the 900 mg dose at the 14-day dosing interval.

In order to maximize the clinical response in children and adolescent PNH patients and to ensure 100% complement blockade, concentration of eculizumab of at least 50 to100µg/ml to completely saturate C5 binding were targeted.

This is consistent with its stoichiometric binding to C5 as eculizumab can bind up to two molecules of C5 and endogenous concentrations of C5 were reported to range from approximately 70 to 90 µg/mL. Since serum eculizumab concentrations of approximately 700 µg/mL have been well tolerated in adult PNH patients following acute and long-term treatments, an upper safety level of 700 µg/mL was used to optimize treatment in adolescent patients. The target eculizumab concentration in PNH paediatric patients is thus >50 µg/mL and <700 µg/mL.

A population PK model of eculizumab was previously developed based on data collected in a total of 177 adult PNH patients from 5 studies (C02-001, C04-001, C04-002, E05-001 and C07-001). A one-compartment model parameterized with clearance (CL) and volume of distribution (Vc) fitted the plasma concentration profiles of eculizumab adequately. Based on this PK model, the following weight-based dosing strategies were proposed for children and adolescent PNH patients (Table 1).

Table 01: PNH Dosing Regimen based on PK Model

Body Weight	Induction / Loading	Maintenance
Children ≥30 kg	600mg Weekly x 4	900mg Wk5; 900mg Q2 Weeks
20 – <30 kg	600mg Weekly x 2	600mg Wk3; 600mg Q2 Weeks
10 – <20 kg	600mg Weekly x 1	300mg Wk2; 300mg Q2 Weeks
5 – <10 kg	300 mg Weekly x 1	300mg Wk2; 300mg Q3 Weeks

Note: Eculizumab was administered via intravenous infusion for 35 minutes.
Source: Table 3 – Protocol M07-005 An Open-Label Multi-center Study of Eculizumab in Children and Adolescents with a Diagnosis of Paroxysmal Nocturnal Hemoglobinuria. 22 October 2010.

The same population PK model was used to determine aHUS paediatric dosing recommendations. These doses have been evaluated in paediatric patients during the development of eculizumab in the aHUS indication (weight ranges from 4.4 to 127 kg) and it was confirmed that the recommended dosing regimen generally resulted as expected in eculizumab concentration between 50 and 700 µg/mL.

The proposed weight-based dosing regimen for PNH paediatric patients was to be evaluated in study M07-005 to confirm that the PK/PD parameters were as expected in this population.

Study M07-005

Methods

Protocol M07-005 was an open-label, multi-center study of eculizumab that was to include six to eight paediatric patients with PNH.

Main inclusion criteria included:

• Individuals from 2 to less than 18 years of age with a diagnosis of PNH

• Patients with >5% GPI deficient red blood cells or granulocytes as confirmed by flow cytometry

• Patients must show evidence of haemolytic anaemia as documented by LDH > ULN or at least one transfusion in the past 2 years for anaemia or anaemia-related symptoms

• Patient must be vaccinated against N. meningitidis, pneumococcus and haemophilus at least 14 days prior to study drug initiation or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination

Treatment with eculizumab for 12 weeks (4-week induction phase and eight weeks maintenance phase) was deemed adequate to assess if the proposed dosing regimen achieved the target therapeutic concentrations in paediatric PNH patients, consistently with the time required to reach at least 95% of average steady state (t0.95) and efficacy assessments at Week 12 were to be performed under steady-state conditions.

The protocol required patients to receive doses of eculizumab intravenously (IV) based on their body weight according to the regimen described in Table 1 for a duration of 12 weeks.

The primary objective of Study M07-005 was to evaluate the PK and PD parameter estimates of eculizumab in order to confirm the dose regimens for paediatric patients with PNH.

The secondary objectives of this study were to assess the safety and efficacy of eculizumab in the treatment of paediatric PNH patients. Efficacy endpoints were change in baseline LDH values, Area under the curve (AUC) of Change in baseline LDH values, changes in plasma-free hemoglobin levels and QoL Assessments. All efficacy endpoints were assessed during the 12-week eculizumab treatment period. In addition, although the number of blood transfusions required was not defined in the protocol as an efficacy endpoint, transfusions are important in the management of PNH, therefore, the number of transfusions before and during eculizumab treatment was assessed.

Therapeutic effectiveness of eculizumab in paediatric PNH patients was assessed by the change in LDH from baseline and the AUC of the change in LDH from baseline up to 12 weeks. Briefly, the changes of LDH from baseline up to 12 weeks (Visits 3-6, 8, and 10) were analyzed using a mixed effect model with time as fixed effect and patient as random effect. The AUC for the change in LDH from baseline up to 12 weeks was calculated for each patient and analyzed using a one sample t-test and nonparametric Wilcoxon signed rank test. Additionally, separate mixed effect models Analysis of Variance (ANOVA) were explored that included individual post-hoc PK parameters derived from the population PK analyses (i.e., predicted AUC, Cmax, Cmin, t1/2, CL, and Vc) of eculizumab as covariates in order to determine whether the changes from baseline in LDH were driven by the exposure to eculizumab. The change in plasma-free haemoglobin measurements from baseline at Week 4 and Week 12 was analyzed using Wilcoxon signed-rank test and one-sample paired-difference t-test.

QoL measurements included the PedsQLTM 4.0 Generic Core Scales (physical, emotional, social, and school functioning) and the PedsQL™ Multidimensional Fatigue questions and scores. In addition, although not specified as an efficacy endpoint in the protocol, a comparison of the number of packed red blood cell (PRBC) transfusion episodes before and after the start of eculizumab treatment was evaluated.

Results

Seven paediatric patients (four females and three males) between 11 and 17 years were treated in Study M07-005. The median age was 15.6 years old. All patients weighed more than 40 kg, with a median weight of 57.2 kg (range of 48.6 to 69.8 kg). These patients represent the intent-to-treat (ITT) patient population that was used in the efficacy analyses.

Patients had a median baseline LDH level of 651 U/L that was approximately twice the ULN of 325 U/L. With the exception of one patient who had normal baseline plasma-free haemoglobin levels, baseline levels were at or greater than the ULN (6.9 mg/dL) for the remaining patients.

One patient had maximum baseline levels of both LDH (3144 U/L) and plasma-free haemoglobin (>60 mg/dL).

All seven patients enrolled received at least one dose of eculizumab and completed 12 weeks of treatment as per protocol. Efficacy analyses were performed on the treated population. Six of the seven patients elected to continue treatment with commercial eculizumab (Soliris) and five of these patients consented to be enrolled in the Soliris PNH Registry (Study M07-001).

- LDH

Change from baseline LDH values at each visit (Visit 3 though Visit 10) showed a rapid and statistically significant reduction in LDH levels that was sustained for the duration of eculizumab treatment in these paediatric PNH patients. As shown in Table 2 mean LDH values from baseline markedly decreased (reduction of 672 U/L) at the time point following the first eculizumab dose and was sustained at all subsequent visits for 12 weeks. The decrease from baseline LDH values after treatment with eculizumab (at Week 12) was statistically significant (P-value=0.0156) based on the Wilcoxon nonparametric test. Results from the paired t-test were also statistically significant (P-Value=0.0336), although the data were not normally distributed (P-Value=0.0031; Shapiro-Wilk test for normality).

Table 02: M07-005: Summary Statistics of LDH Values and Change from Baseline LDH Values by Visit in Paediatric Patients with PNH

Visit (Week)	N=7 (n)	Median (Range) (U/L)	Mean (CV%) (U/L)	Mean Change from Baseline (U/L)
Visit 1 (Screening)	6	639 (404 – 1628)	763 (60.0)	NA
Visit 2 (Baseline)	7	651 (308 – 3144)	1020 (94.9)	0
Visit 3 (Week 1)	7	330 (196 – 633)	348 (39.6)	-672
Visit 4 (Week 2)	7	230 (200 – 374)	257 (24.0)	-763
Visit 5 (Week 3)	7	240 (177 – 459)	268 (37.9)	-752
Visit 6 (Week 4)	7	221 (200 – 387)	259 (31.0)	-761
Visit 8 (Week 8)	7	234 (186 – 421)	272 (36.9)	-747
Visit 10 (Week 12)	7	217 (161 – 376)	248 (29.1)	-771

NA: Not Applicable

A statistically significant (i.e., P-Value < 0.05) decrease in the AUC of the change from baseline LDH was also reported (Table 3).

Table 03: M07-005: Statistical Analysis of AUC for Change from Baseline LDH Values in Paediatric PNH Patients

Mean (SD) AUC of LDH (U·Day/L)	*P*-Value	
	Wilcoxon Signed Rank	Paired t-test[a]
-60634 (72916)	0.0156	0.0350

[a] one-tailed *P*-value

Mixed effect models (ANOVA) were performed to explore whether the decrease in LDH values from baseline in paediatric patients with PNH could be explained by the exposure to eculizumab. Despite the small sample size (n=7), the results of the ANOVA showed that the AUC, Cmax, and Cmin of eculizumab at steady-state were associated with a statistically significant decrease in LDH relative to baseline in patients with PNH for all visits (Table 4). These results are expected, as the exposure to eculizumab, which targets haemolytic activity, is correlated with LDH levels.

Table 04: M07-005: Statistical Analysis (ANOVA) of the Change from Baseline in LDH Values at Visit 3-6, 8 and 10 with PK Parameters of Eculizumab as Covariates in Paediatric PNH Patients

PK Parameter of Eculizumab	Overall *P*-Value
AUC	0.0263
C_{max}	0.0273
C_{min}	0.0250

Post-hoc exposure parameters AUC, C_{max}, and C_{min} of eculizumab at steady-state (maintenance phase)
Source: Excerpt Table 12 of the M07-005 CSR in Module 5

- Plasma-free Haemoglobin

A decreasing trend in plasma-free hemoglobin levels from baseline was observed over the treatment period through Week 12 although the mean decrease was not statistically significant. Mean plasma-free hemoglobin levels were 17.7 mg/dL at baseline and 7.44 mg/dL at Week 12. However, summary values at baseline were skewed by one patient with a value of >60 mg/dL at baseline. This patient's plasma-free hemoglobin decreased to 3.3 mg/dL at Week 12. Median decrease in plasma-free hemoglobin levels for all patients was from 12.7 mg/dL at baseline to 8.4 mg/dL at Week 12.

- PedsQL™ (Paediatric Quality of Life Inventory)

Mixed model analysis was not performed on QoL measurements due to insufficient data collection, including missing data at baseline for some of the patients. Despite the incomplete amount of data available, percent mean change from baseline in the PedsQL™ 4.0 Generic Core Scale scores ranged from 5.4 to 13.3% while the decrease in the PedsQL™ Multidimensional Fatigue scores ranged from -0.52 to -8.84%. • Transfusion Episodes

Six of seven patients (three with a history of aplastic anaemia) received a total of 11 PRBC transfusions before the start of eculizumab. The median haemoglobin value prior to transfusion was 7.0 g/dL and levels ranged from 2.3 to 8.3 g/dL. During the 12 week-treatment with eculizumab, one patient required blood transfusion, which was not unexpected due to underlying aplastic anaemia. Six of seven patients remained transfusion-free throughout the Treatment Period and a marked increase in mean haemoglobin levels from baseline was observed from Week 4 to Week 8.

PK/PD modelling

Pharmacokinetic (PK) and pharmacodynamics (PD) data was previously generated in patients with a diagnosis of paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic-uremic syndrome (aHUS). The goal of this population PK analysis of eculizumab was to support the harmonization of the eculizumab dosing regimen in paediatric PNH patients < 40 kg to the dosing regimen for paediatric aHUS patients < 40 kg as specified in the current Summary of Product Characteristics (SmPC).

Methods

A NONMEM dataset was constructed by merging QA'd population PK datasets previously used for the modelling of eculizumab in PNH and aHUS patients. The population PK analysis was performed with all available PK data for eculizumab in PNH (adults and paediatric patients) and aHUS (adults and paediatric patients), which consisted of a total of 155 PNH patients (Studies C02-001, C04-001, C04-002, E05-001, and M07-005) and 57 aHUS patients (Studies C08-002 A/B, C08-003A/B, and C09-001R).

Population PK modelling of eculizumab was performed to assess the PK in PNH and aHUS patients separately, while leveraging a single allometric function describing the effect of weight on PK parameters.

The one-compartment model was used to bridge PK information in PNH and aHUS patients to support harmonization of dosing in paediatric PNH patients to that in paediatric aHUS patients. The population PK model constructed with PNH and aHUS data was used to derive individual (post-hoc) values of clearance (CL) and volume of distribution (Vc). Individual data were summarized with descriptive statistics (mean, coefficient of variation CV (%), median, range, and sample size).

Descriptive statistics of categorical and continuous demographic data of PNH and aHUS patients used in the population PK analysis are summarized in Table 5 and Table 6, respectively.

Table 05: Characteristics of Patients Included in the Population PK Analysis (Categorical Variables)

Variables		N (%)		
	Categories	PNH	aHUS	Overall
Sex	Male	81 (52.3)	23 (40.4)	115 (54.2)
	Female	74 (47.7)	34 (59.6)	97 (45.8)
Race	Caucasian	137 (88.4)	46 (80.7)	183 (86.3)
	Black	9 (5.8)	5 (8.8)	14 (6.6)
	Asian	6 (3.9)	2 (3.5)	8 (3.8)
	Other	2 (1.3)	4 (7.0)	6 (2.8)
	Unknown	1 (0.6)	0 (0.0)	1 (0.5)
Age Group	**Adult** (≥18 years)	148 (95.5)	8 (14.0)	183 (86.3)
	Paediatric (12 - <18 years) [Adolescents]	6 (3.9)	35 (61.4)	14 (6.6)
	Paediatric (<12 years)	1 (0.6)	14 (24.6)	15 (7.1)

Table 06: Characteristics of PNH and aHUS Patients Included in the Population PK Analysis (Continuous Variables)

Variables		Mean (CV%) Median [Range]		
		PNH	aHUS	Overall
Age (years)		40.3(37.9%) 41[11-85]	25.7(67.6%) 24.2[0.221-69]	36.3(47.1%) 36.5[0.221-85]
Weight (kg)	Adult (≥18 years)	74.1(18.3%) 74[47.6-121]	69.7(26.5%) 68[42-127]	73.2(20.0%) 73.2[42-127]
	Paediatric (12 - <18 years) [Adolescents]	60.9(9.1%) 59.5[55.8-69.8]	56.1(27.7%) 53.4[40.1-91.6]	58.2(20.9%) 56.5[40.1-91.6]
	Paediatric (<12 years)	48.6	16.7(53.2%) 15.9[4.4-38.1]	18.8(63.1%) 19.3[4.4-48.6]
	Overall	73.4(18.6%) 73.3[47.6-121]	54.7(50.2%) 56.2[4.4-127]	68.4(29.4%) 70[4.4-127]

CV%= Percent Coefficient of variation.

The wide range of body weight data available in aHUS patients (4.4 to 127 kg) which is unavailable in the PNH population, allowed for a robust estimation of the relationship between CL and body weight and bridges PK information in PNH and aHUS patients. One paediatric PNH patient below 12 years was included in the analysis. However, the body weight for this paediatric PNH patient (48.6 kg) was markedly higher than the mean body weight observed in paediatric aHUS patients (16.7 kg).

Population PK Analysis results

A total of 2247 concentrations of eculizumab were available to perform this analysis. The distribution of the concentrations over each study and age group is provided in Table 7.

Table 07: Number of Measurable Concentration of Eculizumab Included in the Population PK Analysis

Age Group	N (%)		
	PNH	aHUS	Overall
Adults (≥18 years)	1642 (96.4)	297 (54.7)	1939 (86.3)
Paediatric (12 - <18 years) [Adolescents]	53 (3.1)	58 (10.7)	111 (4.9)
Paediatric (<12 years)	9 (0.5)	188 (34.6)	197 (8.8)
Overall	1704	543	2247

Eculizumab concentration-time data in PNH and aHUS patients were adequately described with the population PK model (goodness-of-fits plots retained on file). Typical values of CL and Vc of eculizumab in PNH and aHUS patients derived with the population PK model are summarised in Table 8.

Table 08: Population PK Parameters of Eculizumab in Adults, Paediatric PNH and aHUS Patients

Population PK Parameters	Typical Values	Between Subject Variability (%)
CL (L/h)	PNH _____	37.4%
	aHUS _____	
Vc (L)	PNH _____	29.6%
	aHUS _____	

CL= clearance of eculizumab; Vc= volume of central distribution of eculizumab

Typical CL values of eculizumab in PNH (weight range: 47.6 – 121 kg) and aHUS (weight range: 4.4 – 127 kg) patients were 0.0202 and 0.0148 L/h, respectively. Typical Vc values of eculizumab in PNH and aHUS patients were 6.94 and 5.85 L, respectively. The power function of body weight on CL estimated with the same allometric function for both populations was 0.795, with a 95% confidence interval of 0.60–0.99, suggesting an important effect of body weight which is in line with the expected theoretical value of 0.75.4 The power function of body weight on Vc was estimated to 0.715 for both populations with a 95% confidence interval of 0.59–0.84.

The relationship between individual CL values and body weight in PNH and aHUS patients are presented in Figure 1

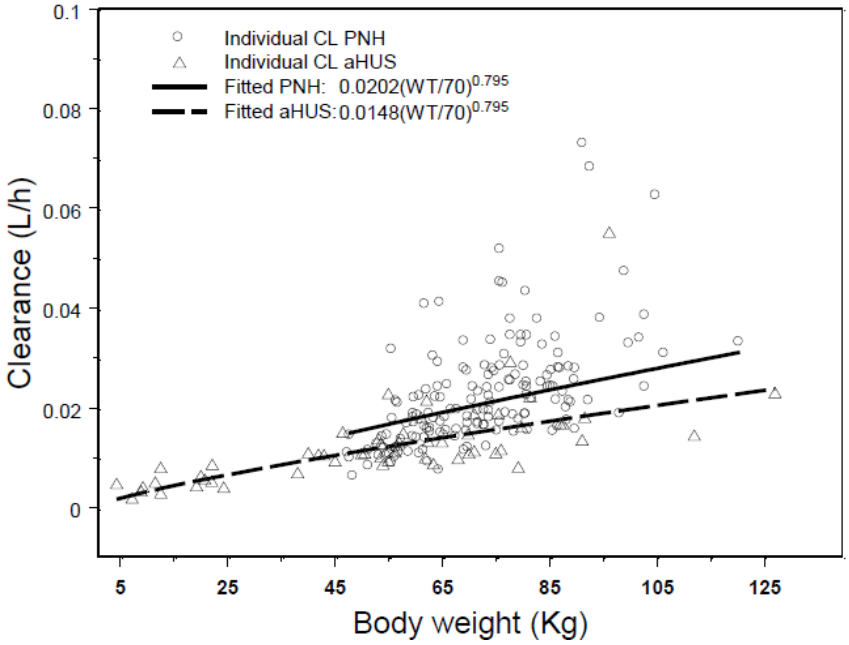

Figure 01: Relationship Between Clearance and Body Weight in PNH and aHUS Patients

The wide range of body weights available in the overall population (4.4 to 127 kg) allowed a robust estimation of the effect of body weight on CL and Vc.

Table 09: Descriptive Statistics of PK Parameters of Eculizumab

PK Parameters	Age Groups	Mean (CV%) Median [Min-Max]	
		PNH	aHUS
CL (L/h)	Adult (≥18 years)	0.0235 (46.0%) 0.0213 [0.00833 - 0.0732] (N=148)	0.0154 (55.1%) 0.0130 [0.00795 - 0.0551] (N=35)
	Paediatric (12 - <18 years) [Adolescents]	0.0105 (25.8%) 0.0104 [0.00727 - 0.0152] (N=6)	0.0124 (23.4%) 0.0116 [0.00921 - 0.0179] (N=8)
	Paediatric (<12 years)	0.0061 [0.00519 – 0.00702] * (N=1)	0.0050 (38.3%) 0.00482 [0.00178 - 0.00849] (N=14)
Vc (L)	Adult (≥18 years)	7.52 (27.3%) 7.22 [3.28 - 15.0] (N=148)	5.86 (28.9%) 5.26 [2.74 - 10.6] (N=35)
	Paediatric (12 - <18 years) [Adolescents]	4.04 (25.6%) 3.87 [2.91 - 5.31] (N=6)	5.46 (25.1%) 5.81[2.69 - 7.18] (N=8)
	Paediatric (<12 years)	2.63 [2.297 – 2.960] * (N=1)	1.98 (41.0%) 1.88 [0.772 - 3.46] (N=14)

CL=individual clearance values divided by the individual body weight; CV%= percent coefficient of variation, Min=minimum, Max=maximum, Vc= individual volume of distribution divided by the individual body weight.
* 95% confidence interval derived based on uncertainty of parameters derived with the population PK model

Adult patients (≥ 18 years) displayed a considerable overlap in individual CL values in the PNH (0.00833 to 0.0732 L/h) and aHUS (0.00795 to 0.00551 L/h) populations. Paediatric patients 12 to < 18 years also displayed a considerable overlap in individual values in the PNH (0.00727 to 0.0152 L/h) and aHUS (0.00921 to 0.0179 L/h) populations. The CL value in the single PNH paediatric patient <12 years (0.0061 L/h) was consistent with the mean value observed in the aHUS paediatric population (0.0050 L/h) and is included in the range of observations (0.00178 – 0.00849 L/h).

Adult patients (≥ 18 years) also displayed a considerable overlap in individual Vc values in the PNH (3.28 to 15.0 L) and aHUS (2.74 to 10.6 L) populations. Likewise, considerable overlap was observed in individual Vc values in the PNH (2.91 to 5.31 L) and aHUS (2.69 to 7.18 L) paediatric patients 12 to < 18 years populations. The Vc value in the single PNH paediatric patient < 12 years was consistent with the mean value observed in the aHUS paediatric population and included in the range of observations (0.772 – 3.46 L).

The wide range of body weights observed in the PNH and aHUS populations (4.4 to 127 kg) allowed for a robust estimation of the effect of body weight on CL and Vc across all age groups and ultimately allowed for the bridging of PK information in PNH and aHUS patients. The above results clearly demonstrate similarity in CL and Vc of eculizumab in PNH and aHUS adults, paediatric 12 to < 18 years, and were also consistent for paediatric <12 years patients. Therefore, PNH and aHUS patients are expected to display similar exposures of eculizumab following administration of similar doses.

2.4.3. Discussion and conclusion on clinical pharmacology

Study M07-005 was initially a PK study aimed to confirm the proposed dosing for children with PNH. The 4 weeks of induction phase and the 8 weeks for maintenance seem adequate for this purpose.

Seven patients were included and treated in the study with eculizumab. The dosing regimens studied were those previously approved for paediatric patients with aHUS <30kg, but with the currently approved dose for adults patients with PNH recommended in this study for children > 30 kg.

Results from this study were consistent with the results and known efficacy profile of eculizumab in adult patients with PNH (reduction of intravascular haemolysis as measured by serum LDH level, elimination of blood transfusions, and an overall improvement in general function). However, considering all patients recruited in this study weighed more than 40 kg, with a median weight of 57.2 kg (range of 48.6 to 69.8 kg), all subjects actually received the dosing regimen for adult patients and no new data in patients <40kg has been provided to support the proposed recommendation in PNH.

As per the current SmPC, dosing recommendations for paediatric aHUS patients are given according to the body weight of patients. As such, it is proposed that the dosing recommendation for paediatric PNH patients should be harmonized to the current body weight-based paediatric aHUS dosing recommendation.

The paediatric dosing recommendations for aHUS paediatric patients have also demonstrated adequate PD activity (close-to-complete inhibition of % haemolysis and reduction in free C5) as well as efficacy and safety of eculizumab treatment for aHUS paediatric patients < 40 kg. At similar eculizumab exposures as aHUS paediatric patients < 40 kg, PNH paediatric patients < 40 kg are therefore expected to display similar PD activity (close-to-complete inhibition of % haemolysis).

Population PK analysis have demonstrated some grade of similarity in CL and Vc of eculizumab for PNH and aHUS patients, both in adult and paediatric patients (12-18 years).

Therefore, considering the efficacy for PNH from available data and that these two apparently different diseases are going to offer a similar response to eculizumab treatment, since the mechanism of action and the implication of eculizumab in the treatment of these two pathologies are basically identical (Soliris being a terminal complement inhibitor that specifically binds to the complement protein C5), the Applicant's proposal is acceptable. The registry M07-001 with PNH patients treated with Soliris will generate and provide to the CHMP periodic updates of available efficacy data in the subset of children <40kg with PNH treated with Soliris.

In addition section 4.1 was updated to reflect the target population of Soliris for PNH in line with the SmPC guideline. This change is also introduced for aHUS although the indication in adults and children was granted on 24 November 2011.

2.5. Clinical safety

2.5.1. Introduction

There are limited studies examining the natural history of PNH in paediatric cases. A retrospective analysis of 26 paediatric cases[1] revealed similarities in the signs and symptoms between childhood and adult PNH including intravascular haemolysis, bone marrow failure and thrombosis.

Paediatric patients with PNH enrolled in Study M07-005 were required to show evidence of haemolytic anaemia as documented by LDH levels greater than the upper limit of normal (ULN) or at least one transfusion in the past two years for anaemia or anaemia related symptoms. Because eculizumab is a terminal complement inhibitor, patients receiving eculizumab are at an increased risk of developing infections caused by encapsulated bacteria including N. meningitidis. To mitigate the risk of these infections, all patients must have been vaccinated against N. meningitidis, S. pneumoniae, and H. influenzae at least 14 days prior to first dose of eculizumab or have been vaccinated and have been receiving treatment with appropriate antibiotics until 14 days after the vaccination.

[1] Ware RE, Hall SE, Rosse WF. Paroxysmal nocturnal hemoglobinuria with onset in childhood and adolescence. N Engl J Med 1991 Oct 3;325(14):991-6.

Safety was assessed by examination of adverse events (AEs), clinical laboratory data, vital signs, and physical examination during the 12 weeks of treatment with eculizumab. Patients continued to be monitored during a follow-up period of eight weeks after last dose of eculizumab.

Patient exposure

Paediatric patients with PNH received a total of nine doses of eculizumab for a median duration of 12 weeks during the study (Table 10). After completion of the study, six of the seven patients in Study M07-005 continued to receive commercial eculizumab.

Table 10: M07-005: Summary of the Extent of Exposure to Eculizumab

Parameter	ITT Population (N=7)
Total Duration of Treatment (weeks)	
Mean (SD)	12.181 (0.2945)
Median (Range)	12.140 (11.71, 12.71)
Total Number of Eculizumab Doses (n)	
Median (Range)	9.0 (9, 9)
Total Amount of Eculizumab Doses (mg)	
Mean (SD)	6857.1 (113.39)
Median (Range)	6900.0 (6600, 6900)

Source: Table 13 of the M07-005 CSR in Module 5.

Table 11: M07-005: Summary of Baseline Characteristics

Clinical Laboratory Values, Median (range)	Overall (N = 7)
LDH (U/L)	651 (308, 3144)
RBC (x 10^{12}/L)	2.72 (1.95, 4.30)
Hemoglobin (g/L)	96.0 (72, 124)
WBC (x 10^{9}/L)	3.40 (3.0, 7.0)
Plasma-Free Hemoglobin (mg/dL)	12.7 (5.3, 60)
Platelet Count (x 10^{9}/L)	70.0 (50, 308)
Transfusion Episode	
Number of patients (n[%]) with at least one Transfusion Episode	6 (86)
Total Number of RBC Transfusion Episodes	11
Proportion (%) of Total Number of RBC Transfusion Episodes Associated with Anemia-related Symptoms	6/11 (55)

Source: Table 6 and Table 7 of the M07-005 CSR in Module 5.

Adverse events

All seven (100%) patients reported at least one treatment-emergent adverse event (TEAE) during the study, and two (29%) patients experienced SAEs. The majority of patients (4 of 7) reported TEAEs that were mild in severity. Overall, eculizumab was well tolerated in paediatric patients with PNH (Table 12).

Table 12: M07-005: Summary of the Number of Patients with Treatment-Emergent Adverse Events by Severity and Relationship to Eculizumab

Parameter	ITT Population (N=7)
Patients with at least one TEAE	7 (100.0%)
Patients with any serious TEAE	2 (28.6%)
Total Number of TEAEs (n)	69
Severity	
Mild	4 (57.1%)
Moderate	1 (14.3%)
Severe	2 (28.6%)
Relationship	
Unrelated	2 (28.6%)
Possible	3 (42.9%)
Probable	2 (28.6%)
Definite	0 (0.0%)

Source: Table 14 of the M07-005 CSR in Module 5.

TEAEs that were reported in ≥2 patients are presented in Table 13 by system organ class and preferred term. A total of 69 TEAEs were reported by all seven (100%) patients enrolled in the study. The remaining TEAEs were each reported by one patient (14%).

Table 13: M07-005: TEAEs Occurring in ≥2 Patients by System Organ Class and Preferred Term

SYSTEM ORGAN CLASS Preferred Term	ITT Population (N=7) Number of Patients (%)
Patients with at Least One TEAE	7 (100.0%)
Total Number of TEAEs (n)	69
NERVOUS SYSTEM DISORDERS	5 (71.4%)
Headache	5 (71.4%)
INFECTIONS AND INFESTATIONS	4 (57.1%)
Upper Respiratory Tract Infection	2 (28.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (42.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (42.9%)
GASTROINTESTINAL DISORDER	2 (28.6%)
Abdominal Pain Upper	2 (28.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (28.6%)
Pyrexia	2 (28.6%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (28.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (28.6%)
Cough	2 (28.6%)

Source: Table 15 of the M07-005 CSR in Module 5.

Adverse events considered related to study drug (probable or possible) were reported by five of the seven patients. There were 2 of 69 (2.9%) TEAEs probably related to eculizumab treatment: upper abdominal pain (severe) and hypotension (mild) each reported by one patient. Upper abdominal pain resolved 15 days after onset with medical treatment and hypotension (single episode that occurred seven days after the first dose of eculizumab) resolved within 24 hours without medical treatment. Patients continued eculizumab treatment while AEs resolved. TEAEs considered possibly related to eculizumab included headache (mild and moderate) reported by two (29%) patients, and anemia, thrombocytopenia, fatigue, pyrexia, pain in extremity, increased blood glucose and decreased appetite

each reported by one patient. Excluding headache, all possibly related TEAEs were mild while thrombocytopenia, fatigue, and blood glucose increased (patient was diabetic) were moderate in severity. Overall, a low number of AEs (2 of 69 [2.9%]) were considered probably related and none were definitely related to eculizumab in Study M07-005.

Serious adverse event / deaths / other significant events

SAEs were summarised by frequency and are presented in Table 14. Two (29%) patients reported a total of 12 SAEs. None of the patients discontinued eculizumab treatment or the trial because of an SAE. Three SAEs, anaemia (mild), thrombocytopenia, and headache (moderate) reported by one patient were judged possibly related to eculizumab. These three SAEs resolved with medical treatment (PRBC transfusion, platelet transfusion and paracetamol, respectively). The PRBC transfusions were transient and consisted of one to two treatments every two weeks for a total of seven PRBC transfusions and platelet transfusions were administered every two weeks for a total of five treatments.

The remaining nine SAEs were unrelated to eculizumab and mild to moderate in severity, with the exception of aplastic anaemia that was severe (patient presented with a history of aplastic anaemia). These SAEs required medical treatment and had resolved by the end of the study, with the exception of one episode of anaemia which remained ongoing.

Table 14: M07-005: Summary of Serious Treatment-Emergent Adverse Events Reported by System Organ Class and Preferred Term

SYSTEM ORGAN CLASS Preferred Term	ITT Population (N=7) Number of Patients (%)
Patients with at least One Serious TEAE	2 (28.6%)
Total Number of Serious TEAE (n)	12
INFECTIONS AND INFESTATIONS	2 (28.6%)
Acute Sinusitis	1 (14.3%)
Catheter Site Cellulitis	1 (14.3%)
Otitis Media Acute	1 (14.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (14.3%)
Anaemia	1 (14.3%)
Aplastic Anaemia	1 (14.3%)
Thrombocytopenia	1 (14.3%)
NERVOUS SYSTEM DISORDERS	1 (14.3%)
Headache	1 (14.3%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (14.3%)
Menorrhagia	1 (14.3%)
Vaginal Haemorrhage	1 (14.3%)

Source: Table 16 of the M07-005 CSR in Module 5.

AEs of special interest

Neisseria meningitidis Infection and Other Infections

There were no meningococcal infections reported in Study M07-005. All patients had been vaccinated against N. meningitidis prior to eculizumab treatment. A total of three patients reported a history of

infection that included abscess limb, cellulitis, infectious mononucleosis, sinusitis, and upper respiratory tract infection. During the conduct of the study, a total of four (57%) patients reported TEAEs for the system organ class “Infections and Infestations”. All infections were mild to moderate in severity and judged unrelated to treatment with eculizumab. Infections included acute sinusitis, catheter site cellulitis, acute otitis media, and upper respiratory tract infection (URTI). Each infection was reported by one patient except URTI, which was reported by two patients. Patients continued treatment with eculizumab while the infections resolved.

Sepsis and Haemolytic Events

None of the patients in Study M07-005 experienced sepsis.

One patient experienced a mild haemolytic event at the end of the follow-up period (Week 8) that was unrelated to eculizumab treatment (elevated LDH value of 371 U/L and reduced haemoglobin value of 98 g/L). This event was attributed to the patient’s underlying PNH disease. Vital signs were within normal limits and no medical intervention (e.g., transfusion) was initiated due to this event. No other haemolytic events were reported in this study.

Laboratory findings

There were no apparent trends in the mean blood chemistry test values over the 12 week Treatment Period. Mean values for blood chemistry tests were within normal limits or marginally outside the upper and lower limits. During the study, one patient had elevated (three times above the upper limit of normal) aspartate aminotransferase (AST) at baseline, which decreased to within normal levels for the remainder of the study. Three patients with AST levels above the normal range at baseline shifted to within the normal range from Week 4 to Week 10.

Overall, mean values for the haematology tests were within normal limits or marginally outside the upper and lower limits of normal except for platelet counts and % reticulocyte. Four patients had platelet count >2-fold below the lower limit of normal and % reticulocytes was >2-fold above the normal range. At baseline and throughout the study, five of seven patients had platelet counts below the normal range while mean % reticulocyte counts were slightly above normal range throughout the study. The overall elevated mean % reticulocyte values may be attributed to one patient with % reticulocyte values three to six fold above the upper limit of normal at Week 2, Week 4, and Week 8.

For WBC count, RBC count and %lymphocyte, levels were >2-fold below the lower limit of normal each in one patient on one or two visits. Shifts from baseline to low or baseline to high were observed in ≥2 patients for lymphocyte, MCV, neutrophil, RBC and WBC. These shifts were sporadic and no trends were observed over the eculizumab Treatment Period.

Median haemoglobin levels increased from 96.0 g/L at baseline to 101 g/L (93-124 g/L) by the end of the study. A marked decrease from baseline in LDH and plasma-free haemoglobin levels were observed during the eculizumab treatment period. LDH and plasma-free haemoglobin values are markers of efficacy and are presented and discussed in section 2.4.

Mean values for the flow cytometry tests (granulocyte PNH clone, PNH monocytes, Type I, Type II, and Type III RBC cells) did not demonstrate any major changes from baseline.

Human Antihuman Antibody (HAHA)

None of the seven patients developed a human antihuman antibody response after 12 weeks of eculizumab treatment. All post-dose results for HAHA were negative (<1.3 µg/mL).

Post marketing experience

A total of 28 patients with PNH below the age of 18 years received eculizumab treatment between 2 April 2011 and 1 April 2012 (as reported in the PSUR covering the same period). Of these, 18 patients experienced AEs that are reported in 42 individual case safety reports. Overall, these cases do not reveal any new safety concern and the safety profile of eculizumab in paediatric PNH population appears similar to the adult PNH population.

2.5.2. Discussion and conclusion on clinical safety

Results from were Study M07-005 were similar to the low number of AEs definitely or probably related to eculizumab in adult PNH patient trails (2.6% in the TRIUMPH trial and less than 8.0% in the SHEPHERD trial).

SAEs of anaemia and headache reported by paediatric patients in this study were also reported in adult PNH patients. Overall, the number of paediatric patients reporting SAEs was low, and consistent with the SAE data reported in adult PNH patients (9.3% of patients in the TRIUMPH trial and 12.4% of patients in the SHEPHERD trial).

There were no obvious trends in clinical laboratory results during treatment with eculizumab and this was consistent with results obtained in adult PNH patients.

HAHA frequency reported in these paediatric PNH patients was also consistent with the low frequency observed in adult PNH patients (none of the 97 patients in the SHEPHERD study developed immunogenicity to eculizumab and weak and transitive immunogenicity results were observed for 2 of 43 [4.7%] patients in the TRIUMPH study).

Therefore, although the sample size of the patients included in the study is limited, the safety profile of eculizumab appears to be similar to that seen in adults. No new risks and/or toxicities have been identified, however for consistency the wording in section 4.4 of the SmPC under “other systemic infections” has been aligned with the wording under “meningococcal infection” to reflect the increased susceptibility of patients to infections.

In order to address the limited data available in PNH patients below 40kg with the proposed regimen, the MAH will generate and provide to the CHMP periodic updates of available safety data in the subset of children <40kg with PNH treated with Soliris and included in the Registry M07-001.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged. The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk management plan

The MAH submitted an updated Risk Management Plan version 7 within this variation procedure.

Some of the minor changes submitted in this updated version are as follows:

- Clinical trial exposure of the PNH clinical study M07-005 and aHUS clinical study (Japan)
- Post marketing exposure
- Update of the PNH and aHUS registries status.

Table 1. Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance activities	Proposed Risk Minimization activities
IDENTIFIED		
Meningococcal infection	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	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. Mandatory vaccination against haemophilus and pneumococcus in children below 18 years of age according to national vaccination guidelines. 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	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**

Safety Concern	Proposed Pharmacovigilance activities	Proposed Risk Minimization activities
Infusion reactions	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**
POTENTIAL		
Serious infections	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**
Immunogenicity	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** Section 2. **Physician's Guide to Prescribing**
Serious haemolysis after drug discontinuation in PNH patients	Routine Pharmacovigilance PNH Registry - Maintained at least 5 years - Includes collecting information for specific events Events of Interest as part	**SmPC** 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**

Safety Concern	Proposed Pharmacovigilance activities	Proposed Risk Minimization activities
	of additional Pharmacovigilance	**PNH** **PNH Patient/Parent information brochure**
Malignancies Hematologic abnormalities in PNH	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.
MISSING INFORMATION		
Pregnancy and lactation	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** **PNH and aHUS Patient/Parent information brochures.**
Children	1. Routine Pharmacovigilance 2. PNH and aHUS Registries 3. Pediatric clinical study C10-003 in aHUS	**SmPC** Specific considerations regarding PNH and aHUS pediatric population are detailed in sections 4.2, 4.4 and 5.2 **Physician's Guide to Prescribing** **Patients information brochures**
Patients with renal impairment	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** **PNH and aHUS Patient/Parent information brochure**
Patients with hepatic impairment	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** **PNH and aHUS Patient/Parent information brochure**
Long term safety in aHUS patients	1. Routine Pharmacovigilance 2. aHUS Registry 3. Clinical studies in aHUS C10-004 C11-003	None

The PRAC, having considered the data submitted, is of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product. The ongoing PNH registry will therefore include both adult and paediatric patients.

No new additional risk minimisation activities were required in addition to those already implemented.

The CHMP endorses this advice without changes.

2.7. Update of the Product information

As a consequence of this extension of the indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated (new text bold, underlined, deleted text strikethrough).

4.1 Therapeutic indication

Soliris is indicated **in adults and children** 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 haemolytic uremic syndrome (aHUS) (see section 5.1).

[...]

4.2 Posology and method of administration

Adult Patients:

In Paroxysmal Nocturnal Haemoglobinuria (PNH):
The PNH dosing regimen **for adult patients (≥18 years of age)** consists of a 4-week initial phase followed by a maintenance phase:

- Initial phase: 600 mg of Soliris administered via a 25 – 45 minute intravenous infusion every week for the first 4 weeks.
- Maintenance phase: 900 mg of Soliris administered via a 25 – 45 minute intravenous infusion for the fifth week, followed by 900 mg of Soliris administered via a 25-45 minute intravenous infusion every 14 ± 2 days (see section 5.1).

~~Paediatric Population~~
~~The safety and efficacy of Soliris in children with PNH aged less than 18 years have not yet been established. No data are available.~~

[...]

Paediatric patients:
Paediatric PNH and ~~In paediatric~~ aHUS patients **with body weight >40kg are treated with the adult dosing recommendations, respectively;**

In paediatric PNH and aHUS patients with body weights below 40kg ~~aged less than 18 years,~~ the Soliris dosing regimen consists of:

Patient Body Weight	Initial Phase	Maintenance Phase
~~≥40 kg~~	~~900 mg weekly x 4~~	~~1200 mg at week 5; then 1200 mg every 2 weeks~~
30 - <40 kg	600 mg weekly x 2	900 mg at week 3; then 900 mg every 2 weeks
20 - <30 kg	600 mg weekly x 2	600 mg at week 3; then 600 mg every 2 weeks
10 - <20 kg	600 mg weekly x 1	300 mg at week 2; then 300 mg every

		2 weeks
5 - <10 kg	300 mg Weekly x 1	300 mg at week 2; then 300 mg every 3 weeks

Soliris has not been studied in patients with PNH who weigh less than 40kg. The posology of Soliris for PNH patients less than 40kg weight is based on the posology used for patients with aHUS and who weigh less than 40kg.

[…]

4.4 Special warnings and precautions for use

[…]

Other Systemic Infections:
Due to its mechanism of action, Soliris therapy should be administered with caution to patients with active systemic infections. **Patients may have increased susceptibility to infections, especially with encapsulated bacteria.** Patients should be provided with information from the Package Leaflet to increase their awareness of potential serious infections and the signs and symptoms of them.
[…]

4.8 Undesirable effects

[…]

Paediatric population
In children and adolescent PNH patients (aged 11 years to less than 18 years) included in the paediatric PNH Study M07-005, the safety profile appeared similar to that observed in adult PNH patients. The most common adverse reaction reported in paediatric patients was headache.
[…]

5.1 Pharmacodynamic properties

[…]

Paediatric ~~aHUS~~ population
Paroxysmal Nocturnal Haemoglobinuria

A total of 7 PNH paediatric patients, with a median weight of 57.2 kg (range of 48.6 to 69.8 kg) and aged from 11 to 17 years (median age : 15.6 years), received Soliris in study M07-005.

Treatment with eculizumab at the proposed dosing regimen in the paediatric population was associated with a reduction of intravascular haemolysis as measured by serum LDH level. It also resulted in a marked decrease or elimination of blood transfusions, and a trend towards an overall improvement in general function. The efficacy of eculizumab treatment in paediatric PNH patients appears to be consistent with that observed in adult PNH patients enrolled in PNH pivotal Studies (C04-001 and C04-002) (Table 3 and 6).

Table 6: Efficacy Outcomes in Paediatric PNH Study M07-005

		P – Value	
	Mean (SD)	**Wilcoxon Signed Rank**	**Paired t-test**
Change from baseline at 12 weeks of LDH	**-771 (914)**	**0.0156**	**0.0336**

Value (U/L)			
AUC of LDH AUC (U/L x Day)	**-60,634 (72,916)**	**0.0156**	**0.0350**
Change from baseline at 12 weeks in Plasma Free Haemoglobin (mg/dL)	**-10.3 (21.13)**	**0.2188**	**0.1232**
Change from baseline Type III RBC clone size (Percent of aberrant cells)	**1.80 (358.1)**		
Change from baseline at 12 weeks of PedsQL™4.0 Generic Core scale (patients)	**10.5 (6.66)**	**0.1250**	**0.0256**
Change from baseline at 12 weeks of PedsQL™4.0 Generic Core scale (parents)	**11.3 (8.5)**	**0.2500**	**0.0737**
Change from baseline at 12 weeks of PedsQL™ Multidimensional Fatigue (patients)	**0.8 (21.39)**	**0.6250**	**0.4687**
Change from baseline at 12 weeks of PedsQL™ Multidimensional Fatigue (parents)	**5.5 (0.71)**	**0.5000**	**0.0289**

~~Overall in pediatric patients with PNH, treatment with eculizumab modified the clinical course of the disease, and is consistent with the therapeutic effectiveness observed in adult patients with PNH.~~

5.2 Pharmacokinetic properties

[...]

Paediatric patients
The pharmacokinetics of eculizumab was evaluated in Study M07-005 including 7 PNH paediatric patients (aged from 11 to less than 18 years).
Weight was a significant covariate resulting in a lower eculizumab clearance 0.0105 L/h in the adolescent patients. Dosing for paediatric patients <40 kg is based on paediatric patients with aHUS.

The Package Leaflet has been updated accordingly.

Minor editorial changes have been included as part of this variation.

Changes were also made to the PI to bring it in line with the current QRD template (version 8.3), which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Eculizumab is currently approved in the treatment of paroxysmal nocturnal haemoglobinuria (PNH) and Atypical haemolytic uremic syndrome (aHUS). Both aHUS and PNH are complement inhibitor deficiency disorders characterised by uncontrolled complement activation.

Up to now, in Paroxysmal Nocturnal Haemoglobinuria, the safety and efficacy of Soliris in children had not been established. Optimal therapeutic alternatives in paediatric patients are lacking. Data from

PNH clinical studies in adults had shown that eculizumab serum concentrations greater than 35 µg/mL blocked serum terminal complement activation and resulted in a rapid reduction in intravascular haemolysis in the majority of patients. However, elevated LDH levels, indicating breakthrough haemolysis and incomplete terminal complement inhibition, were occasionally observed in patients with PNH being treated with the PNH specific dose regimen. Due to this fact, in aHUS patients it was considered critically important to optimise the induction and maintenance dose of eculizumab to maintain complete and sustained terminal complement inhibition and to address the higher free C5 levels observed in patients. Therefore, a higher target trough level was chosen (e.g., ≥50-100 µg/mL). 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. Based on this principles, a weight-based dosing recommendation for children <40kg was proposed for the aHUS population.

On these premises, the study M07-005 was conducted based on the dose regimen already approved for aHUS paediatric patients in children and adolescent with PNH.

Data from the study M07-005 indicate a clinical meaningful response, with reduction of intravascular haemolysis as measured by serum LDH level, elimination of blood transfusions, and a positive trend in the general function. All the patients followed the inclusion criteria and only one child discontinued treatment after 12 weeks.

In addition to that, the Population PK analysis submitted demonstrated some grade of similarity in CL and Vc of eculizumab for PNH and aHUS patients, both in adult and paediatric patients (12-18 years).

Uncertainty in the knowledge about the beneficial effects

The 7 children enrolled in the study were all over 40kg and therefore, only the dosing regimen for adult patients could be tested. The aHUS paediatric regimen now proposed for paediatric PNH patients has therefore not been evaluated in the target population. This is therefore the main uncertainty of this application.

Risks

Unfavourable effects

All seven (100%) patients included in the M07-005 study reported at least one TEAE during the study, and two (29%) patients experienced SAEs. The majority of patients (4 of 7) reported TEAEs that were mild in severity. Headache was the most common TEAE reported in five (71%) of seven patients, followed by upper respiratory tract infection, upper abdominal pain, pyrexia, and cough each reported by two patients (29%).

Two (29%) patients reported a total of 12 SAEs. None of the patients discontinued eculizumab treatment or the trial because of an SAE. Three SAEs, anemia (mild), thrombocytopenia, and headache (moderate) reported by one patient were judged possibly related to eculizumab. These three SAEs resolved with medical treatment (PRBC transfusion, platelet transfusion and paracetamol, respectively).

There were no meningococcal infections reported in Study M07-005. None of the patients experienced sepsis.

Uncertainty in the knowledge about the unfavourable effects

The sample size is very low in this specific group of patients. Only 7 subjects and all of them > 40 kg were recruited into the study.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Data from study m07-005 indicate a clinical meaningful response in paediatric patients with PNH between 11 and 17 years of age and weighing more than 30kg, showing a reduction of intravascular haemolysis as measured by serum LDH level, elimination of blood transfusions, and an overall improvement in general function. Although there are uncertainties related to the extrapolation of the efficacy in adolescents/adults to children with PNH and further, whether the experience gained in children with aHUS disease can support a similar dosing recommendation in PNH, it has to be recognised that in all cases there is a common underlying debilitating and life-threatening disorder characterized by uncontrolled activation of the complement system. Eculizumab is able to block this cascade by binding to human complement protein C5 and the doses and plasma levels needed to reach a sustainable blockade appear well characterised particularly in patients with aHUS.

The Population PK analysis shows some grade of similarity in CL and Vc of eculizumab for PNH and aHUS patients, both in adult and paediatric patients (12-18 years). This fact along with the lack of any safety concern, provides reasonable evidence to accept the aHUS dosing regimen for children also for children with PNH. Additionally, the efficacy of eculizumab in PNH paediatric patients is not expected to be different from that shown in adult patients. Therefore, the proposed dose recommendations for use in paediatric patients with PNH is acceptable.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

There is still a lack of data in children below 40 kg, however, the proposal of accepting the dosing regimen already approved for children with aHUS in PNH children patients, seems reasonable. A specific study in this subset of patients (children <40kg) able to support a different dosing regimen does not seem feasible. Based on the efficacy data available and the Population PK analysis indicating a similarity between PNH and aHUS with regard to CL and Vc, the CHMP considered the Benefit/risk to be positive. There are no safety concerns that could add important uncertainties to this decision, even though, data in this population are scarce. Indeed, a paediatric study with the dosing regimen now proposed is already on going in aHUS subjects, which will allow the opportunity of collecting more data on the safety profile in children.

Finally, there is already an opened registry enrolling patients with PNH worldwide (M07-001). One of the two populations of this registry includes PNH patients of any age, including paediatric patients, that are receiving Soliris. This registry could provide more data on efficacy and safety of eculizumab with the new regimen proposed for PNH paediatric patients.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) accepted		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication of Soliris in the Paroxysmal Nocturnal Hemoglobinuria (PNH) in children. Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC of Soliris to include dose recommendations and additional information available in paediatric patients with PNH as requested by CHMP further to the assessment of ME2 14.2. The Package leaflet has been updated accordingly.

In addition, the MAH took the opportunity to introduce some editorial changes and to update the list of local representatives in the Package Leaflet.

Furthermore, the PI is being brought in line with the latest QRD template version 8.3.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.