26 February 2015
EMA/CHMP/204109/2015
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Soliris

International non-proprietary name: eculizumab

Procedure No. EMEA/H/C/000791/II/0066

Marketing authorisation holder (MAH): Alexion Europe SAS

Note

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

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List of abbreviations

AE	Adverse event
CKD	Chronic kidney disease
CVA	Cerebrovascular accident
eGFR	Estimated Glomerular filtration rate
EORTC	European Organisation for Research and treatment of cancer
ESAP	Epidemiological statistical analysis plan
FACIT	Functional assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
GPI	Glycosylphosphatidylinositol
LDH	Lactate dehydrogenase
MAA	Marketing Authorisation Application
MAVE	Major adverse vascular event
PBRER	Periodic Benefit Risk evaluation report
PNH	Paroxysmal nocturnal hemoglobinuria
QLQ-C30	Quality of Life questionnaire C30
SAE	Serious Adverse Event
TE	thrombotic event
ULN	Upper Limit of normal

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 4 April 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product: **For presentations: See Annex A**	**International non-proprietary name:**
Soliris	eculizumab

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
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	Type II	I and IIIB

The Marketing authorisation holder (MAH) applied for a modification of the indication for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) to extend to all PNH patients regardless of their history of transfusion. Consequently, the MAH proposed the update of sections 4.1 and 5.1 of the SmPC. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH also took the opportunity to correct some typographical errors in the product information.

The requested variation proposed amendments to the Summary of Product Characteristics 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 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.

Protocol assistance

The applicant received Protocol Assistance from the CHMP on 18 October 2012. The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Pierre Demolis

Timetable	Actual dates
Submission date	4 April 2014
Start of procedure:	25 April 2014
Rapporteur's preliminary assessment report circulated on:	20 June 2014
CoRapporteur's preliminary assessment report circulated on:	2 July 2014
Joint Rapporteurs' updated assessment report circulated on:	18 July 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2014
MAH's responses submitted to the CHMP on:	18 September 2014
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	24 October 2014
Joint Rapporteurs' updated assessment report on the MAH's responses circulated on:	14 November 2014
Second request for supplementary information and extension of timetable adopted by the CHMP on:	20 November 2014
MAH's responses submitted to the CHMP on:	18 December 2014
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	5 February 2015
Joint Rapporteurs' updated assessment report on the MAH's responses circulated on:	18 February 2015
CHMP Opinion:	26 February 2015

2. Scientific discussion

2.1. Introduction

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare blood disorder with high morbidity and mortality, clinically defined by the deficiency of the endogenous glycosyl phosphatidylinositol (GPI)-anchored complement inhibitory protein CD59 on the surface of blood cells. CD59 normally blocks the formation of the terminal complement complex (also called the membrane attack complex) on the erythrocyte surface, thereby preventing haemolysis. The pathophysiology of PNH is directly linked to the complement-mediated destruction of the susceptible PNH red blood cells, which results in intravascular haemolysis, the primary clinical manifestation in all PNH patients. PNH is a clonal acquired genetic disease arising from a somatic mutation in the gene pig-A, located in the X-chromosome. Inactivating mutations appear only in a proportion of cells (PNH cells) and this proportion can vary among patients and over time in a single patient.

The estimated prevalence of PNH is 13 cases per million. Patients have an approximately 15 year median survival from its initial diagnosis. PNH is associated with multiple serious morbidities, several of which are potentially life threatening. The common clinical manifestations of PNH are haemolytic anemia, venous thrombosis and deficient haematopoiesis. Excessive levels of cell-free plasma haemoglobin during intravascular haemolysis contribute to platelet activation, procoagulant activity and thromboembolism (TE), the leading cause of mortality in these patients (45%). Anemia is highly variable with hematocrit values ranging from ≤20% to normal. Red blood counts (RBC) are normochromic and normocytic unless iron deficiency has occurred from chronic iron loss in the urine. Granulocytopenia and thrombocytopenia are common and reflect deficient haematopoiesis. Clinical haemoglobinuria is intermittent in most patients and never occurs in some, but hemosidenuria is usually present.

Treatment for PNH depends on the severity of symptoms; patients with few or no symptoms do not require treatment other than folic acid and sometimes iron supplementation to increase red blood cell production; in the anaemic patient with signs of haemolysis, prednisone is often given in an attempt to slow the rate of red blood cell destruction; Patients with acute thrombosis are often treated with thrombolytic therapy (streptokinase, urokinase, or tissue plasminogen activator) and placed on long-term anticoagulation drugs and antiplatelet agents; antithymocite globulin is often used for treating the marrow hypoplasia.. Allogeneic bone marrow transplantation (BMT) which allows the replacement of the defective cells, has been the mainstay of curative therapy for PNH for patients with severe disease (i.e., patients with life threatening thrombosis or dangerously low blood counts) because of the risks of this procedure (15-20% chance of death), however, the majority of PNH patients are not eligible for BMT because they lack a suitable donor. Transfusion therapy is useful for raising the haemoglobin level and also for suppressing the marrow production of RBC during episodes of sustained haemoglobinuria.

Eculizumab is a humanized recombinant monoclonal antibody that binds to the human C5 complement protein and inhibits C5 cleavage to C5a and C5b, preventing the generation of the terminal complement complex C5b-9 and thus blocking complement-mediated cell lysis and activation. The antibody is an $IgG_{2/4}$ kappa immunoglobulin comprised of human constant regions and murine complementarity-determining regions (CDRs) grafted onto human framework light- and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

The clinical development program which investigated the use of eculizumab as a treatment for patients with PNH is based in one pivotal randomized, blinded, placebo controlled study (Study C04-001,

TRIUMPH) and a non-comparative supportive study (Study C04-002, SHEPHERD) demonstrating that the reduction of haemolysis by a complement inhibitor would lead to substantial clinical benefit, as measured by the transfusion history, the stabilization of haemoglobin and improvement in fatigue. Subsequently, Soliris was approved in the EU on 20 June 2007 for the treatment of patients with Paroxysmal nocturnal haemoglobinuria (PNH). However, based on the design of the pivotal study, the indication included the following statement "Evidence of clinical benefit of Soliris in the treatment of patients with PNH is limited to patients with history of transfusions".

This type II variation aims to extend the indication by removing the above statement. The claim is based on the analysis of patients accrued in the PNH registry that was not treated with eculizumab prior to enrolment.
The possible use of the data from the PNH Registry (M07-001) in patients without a history of transfusion was discussed with the Committee for Human Medicinal Products (CHMP) via the Scientific Advice /protocol assistance process. The SAWP in their Advice letter dated October 2012 agreed with the MAH proposal to use the data from the PNH registry to form the basis of a type II variation to update the indication for Soliris.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

The MAH has provided a justification of absence of ERA. Eculizumab is a monoclonal antibody, so it is a protein. According to the Guideline on the environmental risk assessment of medicinal products for human use dated June 2006, proteins are exempted of ERA because they are unlikely to result in significant risk to the environment. Therefore, there is no need to provide an environmental risk assessment for eculizumab in this type II variation.

2.3. Clinical aspects

This type II variation is based on the analysis of patients accrued in the PNH registry that were not treated with eculizumab prior to enrolment. Additional supportive evidence from studies submitted as part of the initial application for marketing authorisation is presented and discussed in the light of the registry data.

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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.

- **Table 1: Tabular overview of clinical studies**

Study	Design	Population	Comments	
PNH Registry M07-001	prospective, observational, non-interventional study	over 1500 patients who have a broad range of symptoms at presentation .	The registry was designed to enrich the population for patients more likely to require a transfusion in the six month treatment period.	
TRIUMPH	Randomized trial -	TRIUMPH enrolled 87 patients (43 patients on eculizumab and 44 patients on placebo) with a history of at least 4 transfusions in the previous 12 months and lactate dehydrogenase (LDH) ≥1.5 times the upper limit of normal (ULN) (key eligibility criteria).	TRIUMPH was pivotal to the original approval of eculizumab	
SHEPHERD C04-002 (SHEPHERD)	Non-comparative study.	The trial enrolled 97 patients who had received at least 1 RBC transfusion in the 24 months prior to eculizumab and had LDH ≥ 1.5 times the upper limit of normal.	Study with less stringent transfusion requirements for incoming patients, submitted as part of the original MA	
E05 - 001	Extension study	Enrolled patients from TRIUMPH and SHEPHERD	Longitudinal analyses	

2.4. Clinical efficacy

2.4.1. Dose response studies

N/A

2.4.2. Main study

PNH Registry

Methods

The PNH Registry is a prospective, observational, non-interventional study.

Study participants

Patients with PNH were eligible to enrol if they had been diagnosed with PNH or have a detectable granulocyte PNH clone. Enrolment was open to patients regardless of disease severity, past or planned treatments, or medical history. An enrolment assessment is completed after obtaining informed consent, with follow-up data collected every 6 months.

The analysis would include all patients enrolled in the PNH Registry who meet the following criteria:

-Entered in the PNH Registry on or before April 30, 2012 based on the May 1, 2012 database download. The April 30, 2012 enrolment cut-point will allow included patients, to have one or more follow-up assessments in the final database download of May 1, 2013. Follow-up assessments are requested every six months.

- Initiated treatment with eculizumab after Registry enrolment or never treated with eculizumab.

- Patients must have reported values for enrolment dates, date of birth, and sex. In addition, for eculizumab-treated patients, date of first eculizumab treatment must also be available.

- At minimum, patients must have a follow-up assessment recorded in the study database.

- Patients must have a granulocyte clone size of >=1%

- In addition, patients must have a baseline LDH of >=1.5 multiples over the upper limit of normal (ULN). In addition to the clinical data entered from patients' medical records at enrolment, patients are asked to complete patient-reported outcomes questionnaires, which include the FACIT-Fatigue and EORTC QLQ-C30, at enrolment and during routine office visits. These quality of life instruments have been validated and were previously used in the original PNH submission

Treatments

Objectives

The primary objectives of the PNH Registry are to collect data: 1) to evaluate safety data specific to the use of eculizumab, and 2) to characterize the progression of PNH as well as clinical outcomes, and morbidities and mortality in eculizumab and non-eculizumab treated patients.

Outcomes/endpoints

Primary endpoint:

Change in LDH from baseline to 6 months between eculizumab treated with no history of transfusion and never treated patients with no history of transfusion reported as absolute changes in LDH values from baseline to 6-month and LDH values at 6-month (as well as 12, 18 and 24 months).
Key secondary endpoints:

Secondary endpoints

Change in Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue score from baseline; Changes in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) including the fatigue component.

Fatigue was assessed using the FACIT fatigue instrument and the fatigue component of the EORTC QLQ-C30 questionnaire.

Quality of life was assessed using the EORTC QLQ-C30 questionnaire as well as physician reported symptoms.

Data on fatigue and quality of life were assessed as changes from baseline to last available assessment. FACIT-fatigue and EORTC QLQ-C30 were assessed as absolute changes (reported as mean and standard deviation) as well as the proportion of patients with clinically meaningful improvement (increase of at least 4 points or more on the FACIT scale or an improvement (decrease for symptoms or increase for functioning scales) of at 10 points or more on the EORTC QLQ-C30).

Major adverse vascular events (MAVE) were reported by patients and were also assessed as events per 100 patient years of follow-up.

Other efficacy parameters included changes in haemoglobin and changes in serum creatinine /eGFR over time.

Sample size

Preliminary feasibility analysis based on the February 1, 2013 PNH Registry monthly download has identified 42 eculizumab-treated patients and 123 never treated patients who fulfilled the inclusion criteria. On average, these patients have over one year's worth of follow-up data in the Registry. The patient counts may increase as focused data cleaning is completed prior to the final database download in May 2013.

Based on this feasibility assessment, power analyses were conducted to detect a statistically significant mean difference between the eculizumab-treated and never treated groups with respect to LDH along with FACIT-Fatigue scale. These projections assume a ratio of eculizumab-treated to never treated patients of 1:3 and a two-sided alpha level of 0.05.

If there are 40 treated patients with LDH data included in the analysis, there would be greater than 90% power to detect a mean difference between the eculizumab-treated and never treated groups of 600 with a standard deviation of 400. There would also be greater than 90% power to detect a mean difference of 400 with a standard deviation of 300.

If there are 25 eculizumab-treated patients with FACIT-Fatigue data included in the analysis, there would be greater than 80% power to detect a mean difference between the eculizumab treated and never treated groups of 12.0 with a standard deviation of 8.0. There would also be greater than 80% power to detect a mean difference of 9.0 with a standard deviation of 6.0.

Randomisation

N/A

Blinding (masking)

N/A

Statistical methods

The primary analysis in this submission was based on a pre-specified subgroup of patients from the PNH Registry. The primary population consisted of patients who entered the PNH Registry without a history of transfusion and were treated with eculizumab prior to any recorded transfusion (referred as "PNH Registry – No Transfusion – Eculizumab", a total of 45 patients) or were not treated with eculizumab (referred as "PNH Registry – No Transfusion - No Eculizumab" a total of 144 patients) throughout the follow-up period in the PNH Registry. Sensitivity analyses for changes in LDH, fatigue score and quality of life were also performed without censoring for RBC transfusion.
The outcomes for the PNH Registry analysis were chosen to be consistent with efficacy endpoints used in the two pivotal trials from the original submission. Primary endpoint was change in LDH from baseline to 6 month. Secondary outcomes were: changes in LDH at 12, 18 and 24 months, change in FACIT-fatigue score, change in EORTC fatigue score, patients reported outcomes, physician reported outcomes, changes in laboratory parameters including haemoglobin serum, creatinine, eGFR and CKD stage. All outcomes are reported as changes relative to baseline in accordance with the Epidemiological and Statistical Analysis Plan (ESAP). Given that collection of PNH Registry data was limited to every 6 months, assessments from the PNH Registry are limited to 6 month intervals. When multiple data points were available, the closest to the target date was selected. For the last available assessment, data points collected after the last clinical assessment date were excluded.

The primary outcome was the mean absolute change from baseline in LDH (U/L) to 6 months of follow-up between eculizumab-treated patients with no recent history of a RBC transfusion and never treated patients with no recent history of a RBC transfusion. The mean percentage change from baseline in LDH will also be calculated and summarized. Mean difference and percentage change in LDH from baseline will also be assessed at 12 months, 18 months, and 24 months of follow-up. In addition, mean difference and percentage change in LDH from baseline to each patient's last available LDH value during follow-up will be assessed. Longitudinal analysis of LDH will also be assessed for eculizumab-treated patients with a recent history of one or more transfusions. Secondary outcomes will be the mean absolute change from baseline to 12 months of follow-up between eculizumab-treated patients with no recent history of a RBC transfusion and never treated patients with no recent history of a RBC transfusion in two patient reported outcomes: 1) FACIT-Fatigue scale and 2) EORTC QLQ-C30 fatigue scale. The mean percentage change from baseline in these two scales will also be calculated. Mean difference and percentage change in FACIT-Fatigue scale and EORTC QLQ-C30 fatigue scale from baseline will also be assessed at 6, 18, and 24 months of follow-up. In addition, mean difference and percentage change from baseline to each patient's last available FACIT-Fatigue and EORTC QLQ-C30 assessment during follow-up will be assessed. The FACIT-Fatigue scale consists of values ranging from 0 to 52. Higher scores indicate less fatigue reported by patients. The EORTC QLQ-C30 fatigue scale ranges from 0-100 with higher scores indicating more fatigue reported by patients. Longitudinal analysis of the FACIT-Fatigue and EORTC QLQ-C30 fatigue scales will also be assessed for eculizumab-treated patients with a recent history of one or more transfusions.

Results

Participant flow

As of 30 April 2012, a total of 1547 patients were enrolled in the PNH Registry of whom 882 never received eculizumab prior to enrolment. Of these patients, 189 had no history of transfusion and met the eligibility criteria of clone size and LDH. These 189 patients form the primary population included in this submission: 45 patients who were treated with eculizumab after enrolment in the PNH Registry and 144

patients who received supportive care without eculizumab (No Eculizumab). A total of 6 (13%) patients discontinued in the eculizumab treatment arm vs 13 (9%) in the no-eculizumab group.

Table 2: Disposition of Patients in the PNH Registry

	No (%) of patients			
	Eculizumab No Transfusion	**No Eculizumab No Transfusion**	**Eculizumab Recent Transfusion**	**Total**
Enrolled	45	144	105	294
In Registry at last follow-up	39 (87)	131 (91)	88 (84)	258 (88)
Discontinued PNH Registry or censored at last follow-up	6 (13)	13 (9)	17 (16)	36 (12)
Reason for discontinuation				
Discontinue eculizumab	3 (7)	--	10 (10)	13 (4)
Bone Marrow Transplant	1 (2)	5 (3)	3(3)	9 (3)
Discontinue other	2 (4)	3 (2)	2 (2)	7 (2)
Death	--	5 (3)	2 (2)	7 (2)

Recruitment

The analysis would include all patients enrolled in the PNH Registry who entered in the PNH Registry on or before 30 April 2012. The enrolment cut-point allowed included patients, to have one or more follow-up assessments in the final database download of 1st May 2013. Follow-up assessments are requested every six months.

Conduct of the study

The study concerns a subset of PNH registry and was conducted according to the registry protocol , no major amendments were noted.

Baseline data

Baseline Demographics and disease Characteristics

Demographics were generally similar between the two groups of patients without a history of transfusion. The vast majority were middle age adults. There were 9 paediatric patients with ages ranging from 12 years to 17 years. Nineteen patients were elderly (>65 years old): two (age 70 and 75 years) in the Eculizumab group, and 17 in the No Eculizumab group.

Patients in the subset of eculizumab had lower median Hb levels (10g/dl vs 12g/dl), higher proportion of patients had history of thrombotic events (29% eculizumab vs 11% no-eculizumab), higher fatigue and dyspnoea scores, among others symptoms.

The vast majority of patients in the eculizumab group had haemolysis and at least one symptom. The majority (92%) of these patients had symptomatic chronic haemolytic anaemia at baseline defined as the physician having reported the presence of abdominal pain, shortness of breath, dysphagia, erectile dysfunction, fatigue or anaemia. Specifically, 43/45 (96%) patients in the Eculizumab group and 130/144 (90%) patients in the No Eculizumab group had at least one of the above listed symptoms at baseline. Laboratory parameters and fatigue scores also indicated that the eculizumab group represented a more severe population at baseline.

Table 3: Clinical Symptoms at Baseline[1] (per ESAP) in Patients with Elevated Haemolysis (LDH≥1.5x ULN) with No History of Transfusion – PNH Registry (M07-001)

Clinical Symptom	Eculizumab No Transfusions (N = 45)	No Eculizumab No Transfusions (N = 144)
Fatigue, n (%)	37 / 41 (90.2)	105 / 136 (77.2)
Haemoglobinuria, n (%)	31/ 40 (77.5)	100 / 136 (73.5)
Abdominal pain, n (%)	27 / 41 (65.9)	57 / 135 (42.2)
Shortness of breath (dyspnoea), n (%)	20 / 41 (48.8)	49 / 134 (36.6)
Anaemia (haemoglobin <100 g/L), n (%)	21 / 45 (46.7)	42 / 144 (29.2)
Dysphagia, n (%)	12 / 41 (29.3)	26 / 135 (19.3)
History of MAVE[2], n (%)	13 / 45 (28.9)	16 / 144 (11.1)
Erectile dysfunction, n (%)[3]	4 / 15 (26.7)	17 / 67 (25.4)
History of TE[4] MAVE, n (%)	11 / 45 (24.4)	12 / 144 (8.3)

[1]Baseline as defined in the ESAP: from the time of initiation of eculizumab treatment in the Eculizumab No Transfusion group or from the time of enrolment in the Registry for the No Eculizumab No Transfusion group. Data from the PNH Registry using the 01 July 2014 data download were used.
[2]MAVE = major adverse vascular event
[3]Percentages of patients reporting erectile dysfunction based on males only.
[4]TE = thrombotic event

Numbers analysed

Patients without a History of Transfusion in the PNH Registry

A total of 189 patients from the PNH Registry formed the basis of this analysis. All of them met the entry criteria with LDH ≥1.5 x ULN and a granulocyte clone > 1%. Forty five patients had no recent history of transfusion and went on to receive eculizumab after enrolment in the PNH Registry and 144 had no history of transfusion and never received eculizumab through the entire follow-up period.

A substantial number of patients were excluded from this analysis (8 patients (18%) vs 45 patients (35%), in eculizumab group vs non-eculizumab group, respectively) given that no LDH values at 6-month were available. This was mainly due to the lack of LDH values at 6months. Other reasons were death or transfusions, but these affected a minority of patients (1 patient and 6 patients in eculizumab vs non-eculizumab treatment arms, respectively) and did not impact on study results substantially. The final analysis is based on 37 eculizumab vs 99 non-eculizumab.

Outcomes and estimation

Changes in LDH

Treatment with eculizumab was followed by a clinically relevant change in LDH values from baseline to 6-month, with most patients showing normal or near normal values. LDH values remained almost unchanged in the no-eculizumab treatment arm.

Table 4: Change in LDH (U/L) at 6-Month - Patients without a History of Transfusion

	PNH Registry Eculizumab No Transfusion	PNH Registry No Eculizumab No Transfusion
	N=37	N=99
Absolute change (U/L)		
Median (min-max)	-1042 (-4215, 597)	-29 (-1128, 1320)
Percent change from baseline (%)		
Median (min-max)	-78 (-92, 66)	-3.5(-71, 200)

In most patients treated with eculizumab, the LDH levels returned to or were close to the normal range at the 6-month time point. In patients with longer follow-up, the LDH levels continued normal or near normal. In the No Eculizumab group patients, LDH levels remain elevated with minimal changes compared to what was reported at baseline.

Changes in Fatigue score

Changes in Fatigue scores were available for 19 out of the 25 patients for whom fatigue was assessed at baseline in the eculizumab treated arm vs 66 in the non-eculizumab arm. Based on data available, treatment with eculizumab showed improvements in mean fatigue scores as assessed by two commonly used scales, with 14 (74%) of the eculizumab-treated patients reporting a clinically meaningful improvement of 4 points or more compared to 22 (33%) patients in the No Eculizumab group. Overall, 117 patients (30 in the Eculizumab treated group and 87 in the No Eculizumab group) had at least one assessment after baseline. In those patients the median time from baseline to last available follow-up was 0.9 and 1.4 years, respectively. At last available assessment the median FACIT score in eculizumab treated patients increased to 44, consistent with minimal evidence of fatigue and it was 41 in the No Eculizumab group.

Changes in haemoglobin

At the 6-month analysis, there was a clinically important increase in the haemoglobin level for eculizumab-treated patients (median increase of 9.0 g/L). In contrast, in patients who did not receive eculizumab, the haemoglobin levels were stable (median increase of 1.0 g/L). This correlates with the effect seen in LDH. As for other endpoints, the number of patients for whom data are available decreases dramatically over time, which is an important weakness.

Changes in renal function

There were limited changes in renal function from baseline to month 6 in adult patients with or without eculizumab treatment as illustrated by the median changes in serum creatinine and eGFR. This was as expected since renal function was essentially normal at baseline. Changes in CKD stages could not be assessed due to the small number of patients with assessment of proteinuria.

Quality of life assessment

Improvement in quality of life measures was documented for Global Health, all five functioning scales and all but three of the other components (financial difficulty, diarrhoea and constipation) of the EORTC QLQ-C30

Overall, more eculizumab-treated patients had a clinically meaningful improvement (improvement of 10 or more point) compared to those who did not receive eculizumab. For Global health, functioning scales, Insomnia, Dyspnea, nausea/vomiting, pain and loss of appetite, the mean change from baseline ranged

from 12.3 to 27.2 in the Eculizumab group and was < 5 in the No Eculizumab group. The largest differences were observed for the functioning components (emotional, social, cognitive, role and physical). Almost half of the eculizumab treated patients reported a clinically meaningful improvement for dyspnea resulting in a mean change of 22.8. It is noted that data were not available for all patients and that this was based on a non-blinded assessment and should be taken cautiously. On the other hand, it is recognised that it reflects clinical practice use and are consistent with other variables.

Overall, resolution of symptoms generally occurred more frequently in patients treated with eculizumab than in those in the control group (No Eculizumab). Haemoglobinuria resolved in most patients on eculizumab while it was still present in the majority of those who did not receive eculizumab. Fatigue was reported by the majority of patients at baseline and at last assessment. Resolution of fatigue was somewhat more common in eculizumab treated patients than in the No Eculizumab group. Resolution of symptoms, specifically abdominal pain, dysphagia, backache and shortness of breath occurred more frequently in the Eculizumab group than in the No Eculizumab group.

Table 5: Physician Reported Outcome - Patients without a History of Transfusion

	No of patients with symptoms/evaluable (%)			
	PNH Registry Eculizumab No Transfusion		**PNH Registry No Eculizumab No Transfusion**	
	Baseline	**Last assessment**	**Baseline**	**Last assessment**
Haemoglobinuria	31/40 (78)	12/36 (33)	100/136 (74)	67/129 (52)
Fatigue	37/41 (90)	26/36 (72)	105/136 (77)	84/129 (65)
Abdominal pain	27/41 (66)	10/36 (28)	57/135 (42)	36/129 (28)
Dysphagia	12/41 (29)	1/36 (3)	26/135 (19)	27/129 (21)
Backache	15/40 (38)	7/36 (19)	26/125 (21)	21/124 (17)
Shortness of breath	20/41 (49)	11/36 (31)	49/134 (37)	33/129 (26)
Easy bruising/bleeding	13/41 (32)	5/36 (14)	41/134 (31)	10/129 (8)
Erectile dysfunction	4/15 (27)	3/18 (17)	17/67 (25)	19/66 (29)
Headache	20/41 (49)	17/36 (47)	48/135 (36)	34/129 (26)

MAVE assessments

History of MAVE was different between eculizumab (29%) and non-eculizumab group (11%). No MAVE events were reported in the eculizumab treated group while 5 events in 4 patients were reported in the non-eculizumab treated arm.

Table 6: MAVE - Patients without a History of Transfusion

	PNH Registry Eculizumab No Transfusion	**PNH Registry No Eculizumab No Transfusion**
	N=45	N=144
Patients with MAVE	0	4(i) (3)
Follow-up (person years)	76.05	279.21
Rate/100 person year	0	1.52

The magnitude of the reduction in the incidence of thrombotic events for a given period of time, the same pre and post-treatment, was provided. Due to the fact that the majority of eculizumab-treated patients initiated treatment soon after enrolling in the Registry, the duration of time for which pre-eculizumab data have been collected is limited (24.85 and 72.65 person-years for the No Transfusions and Transfusion groups, respectively). Prior to initiating eculizumab, 2 patients with no history of transfusion and 6 with a history of transfusion reported MAVE, at rates of 8.05 per 100-person-years and 9.64 per 100-person-years, respectively. One patient in the Transfusion group reported 2 events. Both patients in the No Transfusion group experienced TE MAVE. Four patients with a recent history of transfusion each experienced 1 TE MAVE. There were 106.28 and 285.71 person-years of follow-up after eculizumab initiation in the No Transfusions and Transfusion groups, respectively. Over a total span of 392 person-years on eculizumab treatment, only 1 MAVE was reported, at a rate of 0.25 per person-years for all patients on eculizumab with overall pre-treatment rate of 9.23/100 person-years (for 97.5 person-years) and is statistically significant (p=0.001).

Ancillary analyses

Results from a “responder analysis", regarding change in fatigue i.e. proportion of patients switching from severe to moderate-mild scores for the two scales, for the no-eculizumab and the eculizumab treated groups separately, were submitted (see tables 7, 8).

Table 7

Categorical Analysis of Change in FACIT-Fatigue from Baseline to Last Available Assessment Among Patients in the Eculizumab No Transfusion Group (N=19)

		Last Available Assessment				
		Normal (42 – 52)	Mild (35 – <42)	Moderate (6 – <35)	Severe (0 – <6)	**Baseline Total**
Baseline	Normal (42 – 52)	5 (83.3%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	6 (31.6%)
	Mild (35 – <42)	2 (66.7%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	3 (15.8%)
	Moderate (6 – <35)	6 (60.0%)	1 (10.0%)	3 (30.0%)	0 (0.0%)	10 (52.6%)
	Severe (0 – <6)	0 (NA)	0 (NA)	0 (NA)	0 (NA)	0 (0.0%)
Last Available Total		13 (68.4%)	3 (15.8%)	3 (15.8%)	0 (0.0%)	19 (100%)

Table 8

Categorical Analysis of Change in FACIT-Fatigue from Baseline to Last Available Assessment Among Patients in the no Eculizumab No Transfusion Group (N=69)

		Last Available Assessment				
		Normal (42 – 52)	Mild (35 – <42)	Moderate (6 – <35)	Severe (0 – <6)	**Baseline Total**
Baseline	Normal (42 – 52)	26 (78.8%)	3 (9.1%)	4 (12.1%)	0 (0.0%)	33 (47.8%)
	Mild (35 – <42)	4 (28.6%)	3 (21.4%)	7 (50.0%)	0 (0.0%)	14 (20.38%)
	Moderate (6 – <35)	5 (22.6%)	3 (13.6%)	14 (63.6%)	0 (0.0%)	22 (31.9%)
	Severe (0 – <6)	0 (NA)	0 (NA)	0 (NA)	0 (NA)	0 (0.0%)
Last Available Total		35 (50.7%)	9 (13.0%)	25 (36.2%)	0 (0.0%)	69 (100%)

Additionally, a substantial improvement in fatigue was observed in the Eculizumab subset (median change of +10.0 for FACIT-Fatigue and -22.2 for EORTC fatigue), in contrast to the No Eculizumab subset which demonstrated a median change of 0.0 in both scales.

Furthermore, an updated analysis was performed based on a 01 July 2014 data extract, using the same population of patients and the same analyses as were performed for the original data based on a 01 July 2013 data extract. The inclusion of 1 additional year of data collection yielded results (e.g. changes in LDH, fatigue, targeted adverse events, etc.) consistent with what was previously reported.

Furthermore, consistent with the total population of patients analyzed in the PNH Registry analysis, patients with LDH ratio between 1.5x ULN to 3.5x ULN are at considerable risk for TE (rate of 7.70 TE per 100-patient years from study enrolment to initiation of eculizumab). Following initiation of eculizumab, the rate of thrombotic event (TE) for this same subset of patients decreased to 0 per 100-patient years. In addition, the safety profile of this subset of patients is consistent with the profile of eculizumab in the entire Eculizumab group in the full analysis. These results support the relevance of inclusion of all patients with LDH ≥1.5x ULN in the PNH Registry analysis and importantly, the role of eculizumab treatment in providing clinically meaningful benefit and a favourable benefit/risk profile for patients with PNH across the spectrum of haemolysis as measured by LDH.

To further support the clinically meaningful benefit and safety of eculizumab treatment in patients with PNH with haemolysis at the lowest levels of clinically meaningful haemolysis, a post-hoc analysis has been completed for the subset of patients with LDH between 1.5x ULN to 3.5x ULN without a history of transfusion. The results of this sub-population analysis are comparable to those of the full analysis population. Median LDH values in this subset of the Eculizumab group decreased from 740 U/L at baseline to 332.5 U/L at 6 months (n=14), compared to the No Eculizumab subset (758.5 U/L vs 719.5 U/L, respectively, n=58).

Overall, no new safety signals were observed in an updated safety analysis in patients in the Eculizumab group. The updated safety profile is comparable to what has been previously described in the safety section of the SmPC and consistent with our clinical trials and post marketing data. In fact, based on results from the 01 July 2014 data extract, the No Eculizumab group had higher rates of infections,

impaired renal function, pulmonary hypertension, haemolysis and death relative to the Eculizumab group (Table 20). These results confirm a favourable eculizumab benefit/risk profile in the post-marketing setting for patients with PNH without a history of transfusion and LDH ≥1.5x ULN.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9: Summary of Efficacy for PNH Registry

Title: International PNH Registry				
Study identifier	M07-001			
Design	Prospective, observational, non-interventional study			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	<time> N/A ongoing		
Hypothesis	Superiority			
Treatments groups	eculizumab –treated patients with no history of transfusion	45 patients (out of a total of 189) had no recent history of transfusion and went on to receive eculizumab after enrolment in the PNH Registry		
	never treated patients with no history of transfusion	144 had no history of transfusion and never received eculizumab through the entire follow-up period.		
Endpoints and definitions	Primary endpoint	Change in LDH	Change in LDH from baseline to 6 months between eculizumab –treated patients with no history of transfusion and never treated patients with no history of transfusion	
	Secondary endpoint	Change in fatigue score	Change in Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue score from baseline;	
	Secondary endpoint	Change in QoL EORTC	Changes in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) including the fatigue component	
Database lock				
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat: 45 (eculizumab) / 144 (no eculizumab) Per protocol: 37 (eculizumab)/ 99 (no eculizumab) Data cut off July 2013			
Descriptive statistics and estimate variability	Treatment group	Eculizumab	No eculizumab	
	Number of subject	37	99	
	LDH at 6 month median	-1042	-29	
	(min, max)	(-4215, 597)	(-1128, 1320)	

	Change in FACIT-fatigue (median)	8	0	
	(min, max)	(-8, 32)	(-16, 27)	
	Change in EORTC - fatigue (median) (min, max)	-22 (-67, 11)	0 (-100, 33)	
	Change in haemoglobin (g/L) (min, max)	11.3 (-36, 34)	1.3 (-81.8, 115.2)	
	Changes in EORTC QLQ-C30 (mean, SD) Global Health	15.2 (22.68)	-0.1 (20.06)	

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

PNH Populations Treated with Eculizumab across studies: comparisons based on history of transfusion

In this section, the data are further discussed in the context of the broad range of presentation for patients with PNH, and with particular reference to the history for transfusion, which was used as selection criteria in the design of the original eculizumab studies. Four populations of patients with PNH treated with eculizumab are considered:

- Patients with no history of transfusion (PNH Registry)
- Patients with a history of 0-1 transfusion (SHEPHERD Study)
- Patients with heavy transfusion requirement: SHEPHERD with ≥2 transfusions and (TRIUMPH CSR)

Baseline characteristics, table 10:

Table 10: Key Baseline Characteristics in Patients with PNH Treated with Eculizumab

	PNH Registry Eculizumab No Transfusion	SHEPHERD Eculizumab 0-1 Transfusion	SHEPHERD Eculizumab ≥2 Transfusions	TRIUMPH Eculizumab ≥ 4 Transfusions
	N=45	N=22	N=75	N=43
LDH U/L				
Median (min-max)	1431 (301, 4661)	1991 (808, 3851)	2153 (537, 5245)	2032 (499, 5962)
GPI deficient granulocytes				
Median (min-max)	66 (1, 100)	95 (1,99)	96 (20, 100)	81 (10, 98)
Hemoglobin g/L				
Median (min-max)	100 (59, 160)	91 (59, 116)	9 (5, 13)	103 (68, 120)
FACIT Fatigue				
Median (min, max)	32 (8, 52)	27 (10, 46)	34 (5, 51)	37 (11,52)
EORTC fatigue				
Median (min, max)	44 (0, 100)	56 (0, 89)	44 (0, 100)	33 (0, 100)
MAVE n (%)	13 (29)	5 (23)	37 (49)	9 (21)

Results

Table 11: LDH change across cohorts treated with eculizumab

Table 11: Change in LDH (U/L) at 6 Months in Patients with PNH Treated with Eculizumab

	PNH Registry Eculizumab No Transfusion	SHEPHERD Eculizumab 0-1 Transfusion	SHEPHERD Eculizumab ≥2 Transfusions	TRIUMPH Eculizumab ≥ 4 Transfusions
	N=37	N=22	N=75	N=43
Absolute change (U/L)				
Median (min-max)	-1042 (-4215, 597)	-1793 (-3605, -584)	-1813 (-4678, 931)	-1850 (-4065,-300)
LDH value at 6 month (U/L)				
Median (min-max)	290 (142, 1497)	258 (164, 1079)	277 (98, 2944)	239 (142, 2984)

At the end of the 6-month follow-up in SHEPHERD and TRIUMPH or at last assessment in the never transfused group (the observation period extended to last available data with a median of 1.2 years), the median FACIT score was similar in all groups and ranged from 43 to 48 indicating minimal residual fatigue in the majority of patients. The median improvement was -11 in the TRIUMPH study and -33 in patients without a history of transfusion from the PNH Registry and the SHEPHERD study. However, while fatigue was assessed blinded in the triumph Study, this was not the case for any of the other studies, what might have biased results. Further, within the no transfusion group of the Registry, data were missing for more than half of patients included in this subgroup and the assessment was done at different time points for each individual patient, so that data should be taken cautiously. Fatigue is a common symptom in PNH which may be present if haemolytic activity occurs, independently of its severity and the degree of anaemia. In this context, changes should be interpreted.

Tables **12, 13, 14**: Changes in fatigue score and QoL parameters

Table 12: Change in Fatigue Score at 6-Month in Patients with PNH Treated with Eculizumab

	PNH Registry Eculizumab No Transfusion[a]	SHEPHERD Eculizumab 0-1 Transfusion	SHEPHERD Eculizumab ≥2 Transfusions	TRIUMPH Eculizumab ≥ 4 Transfusions
FACIT Fatigue score	N=19	N=22	N=75	N=43
Median Change (min-max)	8.0 (-8, 32)	13 (-12, 37)	8 (-18, 42)	4 (-5, 28)
Median value (min, max)	44 (12, 51)	48 (13,52)	43 (16, 52)	45 (25, 52)
Patients with clinically important improvement	14/19 (74)	19/22 (86)	47/75 (63)	22/41 (54)
EORTC fatigue score				
Median change (min, max)	-22 (-67, 11)	-33 (-89, 11)	-22 (-89, 44)	-11 (-67, 44)
Median Value (min, max)	22.2 (0, 100)	22 (0, 89)	22 (0, 89)	22 (0, 66)
Patients with clinically important improvement n/N (%)	15/19 (79)	17/22 (77)	52 (69)	28/42 (67)

[a] Assessment was made at last available assessment with a median follow-up of 1.2 years

Table 13: **Changes from Baseline in EORTC QLQ-C30 Quality of Life in Patients with PNH Treated with Eculizumab**

		Mean Change (SD)[a]		
	PNH Registry Eculizumab No Transfusion	SHEPHERD Eculizumab 0-1 Transfusion	SHEPHERD Eculizumab ≥2 Transfusions	TRIUMPH Eculizumab ≥ 4 Transfusions
	N=19	N=22	N=75	N=43
Global Health	15.2 (22.68)	24.2 (3.72)	11.9 (2.7)	10.9 (3.8)
Emotional functioning	20.6 (29.45)	18.2 (5.9)	10.3 (2.4)	7.5 (3.84)
Social functioning	27.2 (29.51)	18.2 (6.75)	15.1 (3.0)	16.7 (3.36)
Cognitive functioning	18.4 (29.34)	15.2 (6.75)	9.1 (2.9)	7.9 (2.68)
Role functioning	23.7 (30.59)	20.5 (7.19)	16.9 (3.2)	17.9 (4.19)
Physical functioning	12.6 (15.22)	12.4 (3.17)	12.0 (2.0)	9.4 (1.62)
Dyspnea	-22.8 (33.43)	-22.7 (8.02)	-14.7 (3.7)	-7.9 (5.99)
Nausea/vomiting	-13.2 (25.81)	-1.5 (1.52)	-6.9 (2.7)	-0.4 (2.98)
Insomnia	-15.8 (25.74)	-16.7 (5.70)	-5.8 (2.6)	-7.9 (5.99)
Pain	-13.2 (26.40)	2.3 (5.9)	-10.7 (3)	-12.3 (4.75)
Appetite loss	-12.3 (25.36)	-12.1 (5.16)	-0.4 (3.0)	-10.3 (3.85)
Financial difficulty	-3.5 (29.18)	3.0 (3.74)	-1.3 (2.2)	-10.3 (3.68)
Diarrhea	-3.7 (19.43	-3.0 (2.09)	-0.9 (2.0)	4.8 (3.86)
Constipation	-1.8 (13.49)	1.5 (3.45)	-2.2 (2.7)	-6.3 (2.84)

[a] Data are presented with mean and SE in the SHEPHERD study

Table 14: **Patients with Clinically Meaningful Changes in EORTC QLQ-C30 in Patients with PNH Treated with Eculizumab**

	No (%) Patients with Clinically Meaningful Improvement			
	PNH Registry Eculizumab No Transfusion[a]	SHEPHERD Eculizumab 0-1 Transfusion	SHEPHERD Eculizumab ≥2 Transfusions	TRIUMPH Eculizumab ≥ 4 Transfusions
	N=19	N=22	N=75	N=43
Global Health	7 (41)	18 (86)	36 (48)	18 (42)
Emotional functioning	14 (74)	10 (46)	32 (43)	15 (36)
Social functioning	12 (63)	12 (54)	38 (51)	23 (55)
Cognitive functioning	11 (58)	9 (41)	33 (44)	14 (33)
Role functioning	11 (58)	13 (59)	42 (56)	22 (52)
Physical functioning	10 (53)	10 (48)	38 (51)	20 (48)
Dyspnea	9 (47)	12 (57)	33 (44)	12 (29)
Nausea/vomiting	10 (53)	5 (24)	14 (19)	6 (14)
Insomnia	8 (42)	12 (57)	27 (36)	14 (33)
Pain	7 (37)	6 (29)	21 (28)	15 (35)
Appetite loss	6 (32)	7 (33)	13 (17)	26 (19)
Financial difficulty	3 (16)	3 (14)	10 (13)	11 (26)
Diarrhea	2 (11)	2 (9)	15 (20)	2 (5)
Constipation	2 (11)	2 (9)	9 (12)	9 (21)

[a] Assessment was made at last available assessment with a median follow-up of 1.2 year

Clinical studies in special populations

Elderly and paediatric patients were included in the PNH registry, no additional clinical trials in special populations have been submitted

Supportive studies

In addition, data from study C04-002 (SHEPHERD) were presented (see above). Relevant data are discussed in the initial MA for a subgroup of 22 patients who had a history of 0-1 transfusion prior to receiving eculizumab. This subgroup provided the first evidence of eculizumab activity in the minimally transfused PNH patient population.

The secondary analysis consisted of a descriptive presentation of the subgroup of 75 patients enrolled in the SHEPHERD trial who had a history of 2 or more transfusions, a group which is largely similar to the TRIUMPH Study patients, which was comprised of patients with a history of frequent transfusion (at least

4 transfusions in 12 months prior to eculizumab). Data from TRIUMPH were used in this submission as a reference supporting the efficacy in heavily transfused patients with at least 4 transfusions in 12 months.

Analyses from Shepherd and Triumph included changes in LDH at 6 months, changes in FACIT-fatigue score at 6 months or last available assessment, and changes in EORTC QLQ-C30 at 6 months or last available assessment.

SHEPHERD Study – Analysis by History of Transfusion

A total of 97 patients were enrolled in the SHEPHERD study. Of these 97 patients, twenty two received either 0 or 1 transfusion in the 12 months prior to enrolment. These 22 patients were considered minimally transfused as opposed to the remaining 75 patients with ≥2 transfusions in the 24 months prior to eculizumab. These 75 patients are similar to those accrued in the TRIUMPH study and represent the group of patients with a history of transfusion who formed the basis for the original approval of eculizumab in PNH. This section of the summary will primarily focus on the 22 patients from the SHEPHERD study with 0-1 transfusion.

Baseline Characteristics

The majority of patients in both groups were young adults with a median age of 45 years. There were 3 patients greater than 65 years old in the group of 0-1 Transfusion and 4 in the group of ≥2 Transfusions. Numbers of males and females were similar.

Patients presented with evidence of haemolysis as illustrated by elevated LDH levels in both groups with a median of 1991 U/L in patients with 0-1 transfusions and 2153 U/L in those with ≥2 transfusions. The majority of patients also presented with GPI deficient granulocytes (95% and 96% in each group) and all patients had various degree of anaemia: median Hb 9.1 g/dl (5.9, 11.6) vs 9.3 g/dl (4.8, 13.1), in the low and high transfusions groups, respectively. Five of the 22 patients in the 0-1 Transfusion group reported 9 MAVE for an event rate of 4.9 events per 100 patient years of follow-up. These events consisted of cerebrovascular accident (4 events in 3 patients), deep vein thrombosis (2 patients), microvascular thrombosis, portal vein thrombosis and transient ischemic attack (one patient each). Among the 75 patients with ≥2 transfusion, 37 patients (49%) reported 82 MAVEs for an event-rate of 15.3 per 100 patient years of follow-up. Prior to eculizumab treatment, the majority of patients presented with clinically important symptoms of fatigue measured by either the FACIT-fatigue scale (median 27 vs 34 in low and high transfusion groups, respectively) or the EORTC QLQ-C30 fatigue subscale (median 56 vs 44 in low and high transfusion groups, respectively). Prior to eculizumab treatment, patients reported clinically important impact on most measures of this instrument. Patients presented with important symptoms such as dyspnoea, insomnia, nausea/vomiting and pain.

In general, based on Hb values, fatigue scores and accumulated rate of thrombotic events, the studied population appears more severe compared to that of the registry with no history of transfusions.

Results

At 6-month, all patients had a significant decrease in LDH level with a median change of -1793U/L ($p<0.0001$) in patients with 0-1 transfusions and -1813U/L ($p<0.001$) in those with ≥2 transfusion. At that time point, the LDH levels were normal or close to normal in the vast majority of patients with a median of 258 U/L and 277U/L in the two groups, respectively. Improvement in LDH levels were maintained throughout the entire study and its extension protocol (Study E05-001). At 1 year, the majority of patients maintained normal or near normal LDH levels with a median LDH of 269 U/L and a range from 183 U/L to 2117 U/Lin patients with 0-1 transfusion. The corresponding median LDH in patients with ≥2 transfusion was also 269U/L.

Fifty one (74%) patients with ≥2 transfusions achieved a clinically meaningful improvement in the FACI-fatigue score and 52 (75%) patients achieved a clinically meaningful improvement in the EORTC fatigue score. The improved fatigue scores was maintained during the entire study and the extension phase (Study E05-001) with a median follow-up of 1.2 years. At last follow-up, the median FACIT score was 41 and the median EORTC fatigue score was 22 in the 0-1 Transfusion group.

Significant improvements were documented in most domains of the EORTC QLQ-C30. The largest improvements were seen in Global Health and dyspnoea. Clinically meaningful improvement was also observed in all functioning scales (physical, emotional, role, social and cognitive). No changes in terms of constipation, diarrhoea, nausea/vomiting, pain, and perception of financial difficulty were seen.

PNH Populations Treated with Eculizumab across studies and comparisons based on history of transfusion are presented in the above section.

Data were further discussed in the context of the broad range of presentation for patients with PNH, and with particular reference to the history for transfusion, which was used as selection criteria in the design of the original eculizumab studies. Four populations of patients with PNH treated with eculizumab are considered: Patients with no history of transfusion (PNH Registry); Patients with a history of 0-1 transfusion (SHEPHERD Study); Patients with heavy transfusion requirement: SHEPHERD with ≥2 transfusions and (TRIUMPH CSR) – see section above. A descriptive comparison of the baseline disease characteristics and results following eculizumab treatment in the 4 cohorts of patients defined on the basis of the history of previous transfusions is presented.

Extension Trial (E05-001)

This was an extension study that enrolled patients from TRIUMPH and SHEPHERD and allowed for longitudinal analysis of the benefits of eculizumab treatment in these patients with PNH. Patients from the placebo arm of the TRIUMPH study initiated eculizumab treatment upon enrolment in the trial. Eculizumab treatment resulted in a statistically significant reduction in TE rate from 7.37 events per 100 patient-years (124 total events) prior to receiving eculizumab treatment, compared to 1.07 events per 100 patient-years in the same patients (3 total events) during eculizumab treatment ($p<.001$). Patients in the placebo group had an event rate of 4.38 events per 100 patient-years during the 26-week placebo treatment period. The importance of these findings reinforce that TE are unpredictable and are the leading cause of death in patients with PNH. Improvement in renal function was also observed during eculizumab therapy. These study results supported a favourable long term treatment benefit/risk profile among a population of patients with LDH ≥1.5x ULN at baseline and a mixed history of transfusions.

2.4.3. Discussion on clinical efficacy

The randomized pivotal trial (TRIUMPH) supporting the original MA for eculizumab was designed to enrich the population for patients more likely to require a transfusion in the six month treatment period and showed that eculizumab significantly decreased the need for transfusion and provided higher frequency of haemoglobin stabilization compared to placebo; a significant and sustained reduction in intravascular haemolysis demonstrated by the reduction in LDH as well as improvement in the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score; a statistically significant improvement in almost all components of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) quality of life questionnaire including global health, all five functioning scales and major symptoms such as fatigue, pain and dyspnoea relative to the placebo group. Consistent to what was described in the TRIUMPH study, most patients in SHEPHERD reported significant

improvement in the components of the EORTC QLQ-C30 quality of life instrument including fatigue, global health, functioning scales and various symptoms.

The first evidence that both the complications of PNH as well as the benefit of eculizumab extend beyond the population of heavily transfused patients comes from the SHEPHERD study which included a small cohort of patients who had 0 or 1 transfusions in the year prior to enrolment. Data from these patients were reported at the Annual Meeting of the American Society of Hematology in 2007. This minimally transfused subgroup of patients presented with clinically important haemolysis and other manifestations of PNH including history of thrombotic events fatigue and decrease quality of life. After eculizumab, these patients exhibited a significant reduction of haemolysis (decrease in LDH), improvement in fatigue (FACIT fatigue scale) and reduction in thrombotic events. Independently, a group of Italian investigators reported on nine patients with PNH who were never transfused and were treated with eculizumab (14). Consistent with data from the clinical trials, these patients had a reduction in haemolysis (median LDH decreased from 1500 U/L at baseline to 356 U/L on eculizumab), increase in haemoglobin and improvement in quality of life. None of these 9 patients experienced a thrombotic event during follow up, although all of them had life-threatening thrombosis prior to eculizumab treatment. In addition the analysis of the two studies (TRIUMPH and SHEPHERD) as well as their extension study (Study E05-001) demonstrated a significant reduction in thrombotic events compared to historical data in the same patients prior to eculizumab as well as an improvement in renal function during eculizumab therapy.

The possible use of the data from the PNH Registry (M07-001) in patients without a history of transfusion was discussed with the Committee for Human Medicinal Products (CHMP) via the Scientific Advice process for protocol assistance. The MAH proposed to identify patients without a recent history of transfusion and to demonstrate that those patients had a burden of disease similar to those requiring transfusion.

Design and conduct of clinical studies

This type II variation is based on the analysis of patients accrued in the PNH registry that was not treated with eculizumab prior to enrolment. All patients accrued prior to 30 April 2012 and met the eligibility criteria were considered. A data cut-off of 01 July 2013 was selected, allowing for a minimum follow-up of six months. An update of these data should be provided.
The PNH Registry (M07- 001) has accrued over 1500 patients who have a broad range of symptoms at presentation. The PNH Registry also serves as an important data source for documenting the burden of disease including morbidities and mortality, clinical outcomes and progression of PNH in eculizumab- and non–eculizumab-treated patients, irrespective of transfusion history. Such a large database also provides an opportunity to investigate specific populations. Clinical and laboratory data also provide the basis for the assessment of key efficacy parameters such as degree of haemolysis and quality of life. Based on the known risk of significant morbidities and premature mortality in PNH and the benefit of treatment with eculizumab in patients with PNH, such a database cannot be replicated in a prospective randomized study which would require a no-treatment control group. All patients accrued prior to 30 April 2012 and met the eligibility criteria; no history of transfusions, no prior treatment with eculizumab, LDH elevation, >1% granulocyte clone size, and at least 6-month FU were considered. A data cut-off of 01 July 2013 was selected, allowing for a minimum follow-up of six months; an update was provided up to the cut –off date of 1st July 2014. Additional supportive evidence from studies submitted as part of the initial application for marketing authorisation is presented and discussed in the light of the registry data.

Efficacy data and additional analyses

A subset of 189 out of the 1547 patients included in the registry fulfilled eligibility criteria: no history of transfusions, no prior treatment with eculizumab, LDH elevation, >1% granulocyte clone size, and at

least 6-month FU. Of them, 45 started eculizumab treatment after inclusion while 144 did not received eculizumab. Main efficacy results from the Registry show that in the group treated by eculizumab a clinically meaningful decrease of LDH is observed (-1042 [-4215, 597]); along with an improvement of scores reflecting fatigue is observed (FACIT-fatigue score: +8 [-8; 32]; EORTC-fatigue score: -22[-67; 11]); an increase of hemoglobin level from 100 to 113 g/L is observed.

No major sign of deterioration of the condition is observed in the group that did not receive eculizumab as levels of LDH, hemoglobin, fatigue scores are maintained, suggesting that these patients did not need the treatment with eculizumab.

The comparison of patients treated with eculizumab to those maintained on supportive care in the Registry (no Eculizumab group) demonstrated a statistically significant reduction of haemolysis documented by the reduction in LDH, a clinically important improvement in fatigue and an improvement of all relevant domains on the EORTC QLQ-C30 quality of life assessment in favour of the Eculizumab treated group.
However, this analysis has some limitations, otherwise not unexpected from a Registry, which makes interpretation of results not so straightforward. The groups of comparison within the registry (patients with no history of transfusions on eculizumab vs not on eculizumab) were not randomly selected and thus there are some differences between the groups of comparison in baseline disease characteristics which overall indicate that patients in the eculizumab treated group had a more severe disease. Despite the pre-specified statistical analysis plan and the planned assessments every 6-month, there were a number of missing evaluations,; For LDH, 37 of 45 eculizumab treated nontransfused patients had values reported at 6 months follow-up. However there were a number of patients who did not complete the patient reported outcome assessments of FACIT-Fatigue and EORTC Fatigue; considering the limited numbers of patients, this is of concern. In addition, assessment was not blinded, which might have biased evaluation of subjective endpoints such that fatigue, dyspnoea, QoL, other related symptoms.

Further, the Triumph study that included patients with severe haemolysis (defined by the presence of symptomatic anaemia that required frequent transfusions) showed that by mitigating haemolysis a clear clinical benefit for the patients as measured by stabilization of anaemia (and thus reducing transfusions), related symptoms, and preventing associated morbidity in PNH was demonstrated. Also a reduction in the accumulated rate of thrombotic events, which are usually linked to haemolytic anaemia, the main cause of morbi-mortality in PNH, was shown.

A comparison of the effects in different cohorts of patients from different studies but defined on the basis of prior transfusions is presented. Data were further discussed in the context of the broad range of presentation for patients with PNH, and with particular reference to the history for transfusion, which was used as selection criteria in the design of the original eculizumab studies. Four populations of patients with PNH treated with eculizumab are considered: Patients with no history of transfusion (PNH Registry); Patients with a history of 0-1 transfusion (SHEPHERD Study); Patients with heavy transfusion requirement: SHEPHERD with ≥2 transfusions and (TRIUMPH CSR). A descriptive comparison of the baseline disease characteristics and results following eculizumab treatment in the 4 cohorts of patients defined on the basis of the history of previous transfusions was presented. These data indicate that treatment with eculizumab mitigates intravascular haemolysis, as measured by median LDH change. Patients with PNH in all four groups displayed an important improvement in fatigue.

It is therefore argued that the baseline disease characteristics of the cohort of patients without history of transfusions and who started eculizumab treatment after entering the Registry are indicative of a more serious condition compared to those not on eculizumab, as defined by the presence of a more intense haemolysis, lower haemoglobin levels, more patients with history of MAVE, more patients with clinically

relevant fatigue or presence of other relevant symptoms like dyspnoea or abdominal pain. Results, with the caution needed given the limitations noted above, are indicative of clinically relevant changes in associated morbidity in patients treated with eculizumab. While the focus on patients with haemolysis is reasonable, the proposal to define the severity of the haemolysis based on a single laboratory parameter is not considered appropriate as it is far away from the general clinical practice. LDH>1.5 ULN appears too low and unspecific to be acceptable as the only criteria to guide treatment and define the target population for eculizumab. LDH by itself is not considered an optimal tool when it comes to judge the severity of the disease. An acceptable indication should clearly reflect the PNH population where a positive benefit/risk balance can be concluded based on the data provided and also considering the current knowledge of the disease. An intense haemolysis should be present, but should not be the only criteria, as this might well be rather benign. Therefore, and in line with the evidence available, additional considerations like the presence of relevant symptomatology (e.g. anaemia, dyspnoea, fatigue, abdominal pain, etc) and/ or thrombotic complications should be required. In this sense, the indication should be defined on the basis of the presence of symptoms in SmPC section 4.1. The relevant information on clinical symptomatology of the included population is clearly reflected in Section 5.1 to provide useful information for prescribers.

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~~ **demonstrated** ~~to~~ **in** patients with ~~history of transfusions~~ **haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1)**.
- Atypical haemolytic uremic syndrome (aHUS) (see section 5.1).

2.4.4. Conclusions on the clinical efficacy

The efficacy of Soliris is shown in patients with paroxysmal nocturnal haemoglobinuria (PNH) independently of prior transfusions who present with haemolysis and display relevant clinical symptoms. The data presented can support amendment of the indication of PNH is therefore amended as follows:

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~~ **demonstrated** ~~to~~ **in** patients with ~~history of transfusions~~ **haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1)**.

2.5. Clinical safety

Introduction

The safety profile of Eculizumab in the treatment of PNH is well characterised. The most commonly reported adverse reactions in eculizumab treated patients are headache, nasopharyngitis, nausea, pyrexia, myalgia, fatigue, and herpes simplex. Eculizumab treatment did not seem to be associated with an increase in severity of AEs in treated patients. No cumulative, irreversible toxicities have been reported.

Patient exposure

The evaluation of safety in the treatment of patients with PNH is based on two analyses: analysis based on data from PNH Registry patients with no history of transfusion and data from Alexion sponsored clinical studies – minimally transfused patients from SHEPHERD study and heavily transfused patients from TRIUMPH study. This report summarizes the safety events which were reported and analyzed from the following populations (targeted adverse events, treatment emergent adverse events (TEAEs)), thrombotic events (TEs), death, malignancies etc.).

- Data collected from patients in the PNH Registry (up to data download 1 July 2013), who met the eligibility criteria for the analysis and were categorized based on their history of transfusion requirement and their exposure to eculizumab. The primary analysis to support safety and efficacy of eculizumab in patients without a history of transfusion was conducted on the 45 patients without transfusion who received eculizumab and the 144 patients who remained untreated in the PNH Registry. As the PNH Registry is an observational study, no dosing regimen is specified. Patients are dosed as per physician discretion as part of their normal care. However, there is no reason to expect this dosing to be different than as specified in the Summary of Product Characteristics (SmPC). Duration of eculizumab treatment, and hence cumulative exposure, was a median of 1.3 (0.1 to 3.4) years in patients with no history of transfusion. 3 patients discontinued eculizumab due to BMT (2 patients) and pregnancy (1 patient). Eculizumab median last dose 900mg (600mg – 900mg)
- Data from the minimally transfused sub group of patients (defined as 0 to 1 transfusion in the 12 months prior to eculizumab initiation) from the Alexion sponsored SHEPHERD study (C04-002) are also described. The minimally transfused subgroup analysis of eculizumab-treated patients includes 22 patients out of the total 97 patients enrolled in the SHEPHERD study.
- Data from the heavily transfused (defined as ≥ 2 transfusion in the 12 months prior to eculizumab initiation) patients with PNH from Alexion sponsored TRIUMPH study (C04-001). This study was a randomized placebo controlled study and the data presented here includes the 43 eculizumab-treated patients.

Eculizumab-treated patients with no history of transfusion had a lower mean and median age. A total of 9 paediatric patients (age < 18 at baseline) were in the analysis population; 6 in the no-eculizumab group and 3 in the treated group

Adverse events

Targeted adverse events analyzed for the PNH Registry patients with no history of transfusion included impaired renal function, impaired hepatic function, infections including meningococcal infection, malignancy, thrombotic events, haemolysis, infusion reaction, death, PHT, pregnancy and immunogenicity testing.

From Triumph and Shepherd: Treatment emergent adverse events (TEAEs) for the minimally transfused SHEPHERD patients and eculizumab-treated TRIUMPH patients were summarized by relationship. In addition SAEs for these 2 groups were also summarized by severity.

PNH Registry

Patients in the no-eculizumab group reported a higher rate of infection, MAVE, death and haemolysis. All other events were reported at comparable frequencies between the two groups. Impaired renal function was the most commonly reported targeted adverse event; 9.0% of the no-eculizumab patients reported this event compared to 6.7% of eculizumab-treated patients. These targeted adverse events are as expected for this patient population and are consistent with the current eculizumab SmPC.

Table 15: Targeted adverse events in the PNH registry

Table 15: Targeted Adverse Events Reported During Follow-up in PNH Registry – Sensitivity Analysis

Parameter N (%)	No Eculizumab No Transfusion N= 144	Eculizumab No Transfusion N= 45
Infections	7 (4.9)	0 (0.0)
Meningococcal infections	0 (0.0)	0 (0.0)
All MAVE	4 (2.8)	0 (0.0)
Person-years	279.2	76.1
Rate per 100 person-years	1.8	0.0
All TE MAVE	3 (2.1)	0 (0.0)
Deaths	5 (3.5)	0 (0.0)
Hemolysis	12 (8.3)	1 (2.2)
Impaired renal function	13 (9.0)	3 (6.7)
Pulmonary Hypertension	3 (2.1)	1 (2.2)
Impaired hepatic function	2 (1.4)	1 (2.2)
Infusion reactions	NA	1 (2.2)
Malignancies	4 (2.8)	1 (2.2)
Bone Marrow Transplant	5 (3.5)	1 (2.2)

NA = not applicable.
NOTE: Censoring for RBC transfusion during follow-up was not performed for this analysis.
Source: PNH Registry Report

Among patients in the sensitivity analysis (i.e. not censored for transfusion), 7 patients in the no-eculizumab group reported infections that include pneumonia, and influenza. Four patients in the no-eculizumab group and 1 patient in the eculizumab-treated group reported malignancy. Lung metastasis from breast carcinoma reported in one case (no-eculizumab group) was fatal. All the other malignancies were not fatal and were ongoing at the time of data download.

Pulmonary hypertension reported by 3 patients in the no-eculizumab group and 1 eculizumab treated patient. None of the patients reported meningococcal infection.

SHEPHERD and TRIUMPH Studies

Table 16: Overview of adverse events in SHEPHED and TRIUMPH

	SHEPHERD Eculizumab 0-1 transfusion (N=22)	TRIUMPH Eculizumab ≥ 4 transfusions (N=43)
Overall number of TEAE	223	226
Number (%) of patients reporting:		
at least 1 TEAE	21(95.5)	43(100)
at least 1 SAE	3 (13.6)	4 (9.3)
Number (%) of patients who died	0 (0)	0 (0)
Patients (%) who withdrew due to a TEAE	0 (0)	1(2.3)
Total number of SAEs	4	4
Number of TEAEs[a] (%) rated as:		
Mild	179 (80.3)	190 (84.1)
Moderate	41(18.4)	31(13.7)
Severe	3 (1.3)	5 (2.2)
Number of TEAEs[a] (%) rated as:		
Unrelated	166 (74.4)	166 (73.5)
Possibly related	40 (17.9)	52(23.0)
Probably related	15 (6.7)	7 (3.1)
Definitely related	2 (0.8)	1(0.4)

[a] Severity and relationship to study drug are on a per-event occurrence basis rather than on a per-patient basis

Source SHEPHERD Subgroup Analysis and TRIUMPH CSR

In the 22 minimally transfused patients from the SHEPHERD Study, 57 TEAEs reported by 13 patients, were considered related to eculizumab. Fifty-five TEAEs, reported by 12 patients, were considered possibly or probably related to eculizumab. One patient reported 2 TEAEs considered definitely related to eculizumab. The most common system organ class TEAE deemed related to eculizumab treatment was nervous system disorders (40.9%). Musculoskeletal and Connective Tissue Disorders (22.7%), Gastrointestinal Disorders (18.2%), General Disorders and Administration Site Conditions (13.6%) and Infections and Infestations (13.6%) were other common TEAE deemed related to eculizumab treatment that each accounted for ≥10% of all TEAE.

In the heavily transfused 43 patients from TRIUMPH study, 24 patients reported TEAE deemed related to eculizumab. Only 1 patient reported an event as definitely related TEAE (severe headache after receiving eculizumab infusion; event resolved the day after onset). The most commonly related TEAE was headache.

Table 17: Treatment emergent adverse events – SHEPHERD and TRIUMPH

	SHEPHERD Eculizumab 0-1 transfusion (N=22)	TRIUMPH Eculizumab ≥ 4 transfusions (N=43)
Total number of events[a]	**57**	**60**
Total number of patients[b]	**13**	**24**
System Organ Class[c] **N (%)**		
Blood and lymphatic system disorders	1 (1.8)	1(1.7)
Endocrine disorders	1(1.8)	0 (0)
Eye disorders	1(1.8)	1 (1.7)
Gastrointestinal disorders	4 (7.0)	4 (7.0)
General disorders and administration site conditions	3(5.3)	5 (8.3)
Hepatobiliary disorders	0 (0)	0 (0)
Immune system disorders	0 (0)	1(1.7)
Infections and infestations	3 (5.3)	6(10.0)
Investigations	0 (0)	0 (0)
Metabolism and nutrition disorders	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders	5 (8.8)	2 (3.3)
Nervous system disorders	9 (15.8)	16 (26.7)
Psychiatric disorders	1 (1.8)	0 (0)
Renal and urinary disorders	0 (0)	0 (0)
Reproductive system and breast disorders	0 (0)	1(1.7)
Respiratory, thoracic and mediastinal disorders	2 (3.5)	1(1.7)
Skin and subcutaneous tissue disorders	1(1.8)	3 (5.0)
Vascular disorders	1(1.8)	1(1.7)

[a] Only one of the most related TEAEs per patient within each system organ class was counted.
[b] Only the most related TEAE was counted.
[c] Only one of the most related TEAEs per patient within each system organ class was counted
Source: SHEPHERD Subgroup Analysis and TRIUMPH CSR

Serious adverse event / deaths / other significant events

PNH Registry

Five deaths were recorded in the no-eculizumab group, one was of unknown cause, four were due to underlying conditions; heart failure, uro-sepsis, breast cancer, ischemic heart disease/chronic obstructive airway disease/ injury.

Serious adverse events (SAEs) reported to the pharmacovigilance database include one death in the eculizumab-treated group with no history of transfusion.

SHEPHERD and TRIUMPH Studies

- Deaths

No deaths were reported in the 22 minimally transfused patients during the SHEPHERD study. There were also no deaths reported in the 43 eculizumab-treated patients in the TRIUMPH study.

- Serious Adverse Events

In the minimally transfused 22 patients from the SHEPHERD study, 3 patients (14%) experienced a total of 4 SAEs. Two moderate and two severe SAEs were reported, one each for Gastrointestinal Disorders, General Disorders and Administration Site Conditions, Hepatobiliary Disorders and Nervous System Disorders. The two severe SAEs were headache/increasing headache (SOC Nervous System Disorders) and pyrexia/fever of unknown origin (SOC General Disorders and Administration Site Condition

classified). Both were considered possibly related to drug. The moderate SAEs were both unrelated to drug and classified as cholelithiasis and abdominal pain.

Four patients reported one SAE each in the eculizumab-treated patients from the TRIUMPH study. SAEs in both the SHEPHERD and TRIUMPH patients largely consisted of single-incident events, with limited differences between the 2 groups.

In 3 out of the 5 death cases in the group of patients not receiving eculizumab, death appears not related to the PNH underlying condition. In one case the cause of death in unknown and the remaining appears closely related to the PNH condition. Data on treatment discontinuations are not of concern. Only one death was reported in the eculizumab treatment arm that occurred after eculizumab discontinuation (6-month apart). Differences in the absolute number of deaths are not conclusive given the low number of cases and the different in patients-exposure

Concerning AEs, only top line results from targeted AEs and SAE has been presented. Safety profile appears in line with that known for this population and for eculizumab treatment. There were some differences between treatments of comparison in the absolute incidence of some relevant AEs but given the different observational periods and number of patients at risk, no conclusions can be drawn. Cumulative data should be provided. Further, changes in the incidence of MAVE pre and post inclusion in the registry for the two groups and for a similar period of time should be provided. These data have been provided and, with caution given the limited number of events and different follow up duration, appear to show a benefit in the reduction of thrombotic events.

Laboratory findings

The only information provided has been presented and discussed previously in the AR in relation to efficacy.

Safety in special populations

Table 18 Special Population: SHEPHERD Study 0-1 Transfusions

MedDRA Terms	Age <65 N=19 (86.4% of total)	Age 65-74 N= 2 (9.1% of total)	Age 75-84 N= 1 (4.5% of total)	Age 85+ N= 0 (0% of total)
Total AEs	196	20	7	0
Serious AEs – Total	4	0	0	0
Fatal	0	0	0	0
Hospitalization/prolong existing hospitalization	4	0	0	0
Life-threatening	0	0	0	0
Disability/incapacity	0	0	0	0
Other (medically significant):	0	0	0	0
AE leading to drop-out	0	0	0	0
Psychiatric disorders	4	1	0	0
Nervous system disorders	9	2	1	0
Accidents and injuries	0	0	0	0
Cardiac disorders	1	1	0	0
Vascular disorders	1	0	0	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	17	2	1	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0

MedDRA Terms	Age <65 N=19 (86.4% of total)	Age 65-74 N= 2 (9.1% of total)	Age 75-84 N= 1 (4.5% of total)	Age 85+ N= 0 (0% of total)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	1	2	0	0
Other AE appearing more frequently in older patients				
Constipation	1	1	0	0
Chest discomfort	1	1	0	0
Oedema peripheral	2	0	1	0
Heart rate irregular	0	0	1	0
Rash	0	0	1	0
Somnolence	0	0	1	0
Gastroenteritis	0	0	1	0
Skin lesion	0	1	0	0
Gastroenteritis viral	0	1	0	0
Loose stools	0	1	0	0
Faeces discoloured	0	1	0	0
Dyspepsia	0	1	0	0
Insomnia	1	1	0	0
Headache	9	2	0	0
Dizziness	1	2	0	0
Pain in extremity	2	1	0	0
Muscle cramp	1	1	0	0
Upper respiratory tract infection	6	0	1	0
Decreased appetite	0	1	0	0
Nasopharyngitis	8	2	0	0
Nausea	5	1	0	0
Palpitations	1	1	0	0

Available information from all studies submitted (Triumph, Shepherd, Registry), is provided which include very limited data in the elderly: a total of 15 patients over 65 years old, 4 patients over 75 years old. Safety In the PNH registry only 2 patients over 65 years old were included in the eculizumab treated arm.

Table 19: Safety in Special Populations: PNH registry Eculizumab No Transfusion

MedDRA Terms	Age <65 N= 43 (95.6% of total)	Age 65-74 N= 1 (2.2% of total)	Age 75-84 N= 1 (2.2% of total)	Age 85+ N= 0 (0% of total)
Total AEs	NC	NC	NC	NC
Serious AEs – Total	NC	NC	NC	NC
Fatal	0	0	0	0
Hospitalization/prolong existing hospitalization	NC	NC	NC	NC
Life-threatening	NC	NC	NC	NC
Disability/incapacity	NC	NC	NC	NC
Other (medically significant)	NC	NC	NC	NC
AE leading to drop-out	NC	NC	NC	NC
Psychiatric disorders	NC	NC	NC	NC
Nervous system disorders	NC	NC	NC	NC
Accidents and injuries	NC	NC	NC	NC
Cardiac disorders	NC	NC	NC	NC
Vascular disorders	2	0	0	0
Cerebrovascular disorders	NC	NC	NC	NC
Infections and infestations	0	0	0	0
Anticholinergic syndrome	NC	NC	NC	NC
Quality of life decreased	NC	NC	NC	NC
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	NC	NC	NC	NC
Other AE appearing more frequently in older patients	0	0	0	0

NC = Not Collected

Table 20: Safety in special populations: PNH No Eculizumab No Transfusion

Table 26 Safety in special populations: PNH No Eculizumab No Transfusion

MedDRA Terms	Age <65 N=127 (88.2% of total)	Age 65-74 N= 11 (7.63% of total)	Age 75-84 N= 6 (4.16% of total)	Age 85+ N=0 (0% of total)
Total AES	NC	NC	NC	NC
Serious AEs – Total	NC	NC	NC	NC
Fatal	0	3	2	0
Hospitalization/prolong existing hospitalization	NC	NC	NC	NC
Life-threatening	NC	NC	NC	NC
Disability/incapacity	NC	NC	NC	NC
Other (medically significant)	NC	NC	NC	NC
AE leading to drop-out	NC	NC	NC	NC
Psychiatric disorders	NC	NC	NC	NC
Nervous system disorders	NC	NC	NC	NC
Accidents and injuries	NC	NC	NC	NC
Cardiac disorders	NC	NC	NC	NC
Vascular disorders	5	0	2	0
Cerebrovascular disorders	NC	NC	NC	NC
Infections and infestations	14	0	0	0
Anticholinergic syndrome	NC	NC	NC	NC
Quality of life decreased	NC	NC	NC	NC
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	NC	NC	NC	NC
Other AE appearing more frequently in older patients				
Malignancies	3	1	0	0
Impaired renal function	22	0	6	0
Pulmonary hypertension	5	2	0	0
Haemolysis adverse outcome reported	15	0	2	0

NC=Not Collected

Safety related to drug-drug interactions and other interactions

No such data have been submitted in the context of this variation

Discontinuation due to adverse events

No discontinuations due to AEs were reported in the group of patients with no transfusions from the Registry that form the basis of the current variation.

Post marketing experience

Data supporting the current variation comes from a Registry, which is reflective of postmarketing experience.

2.5.1. Discussion on clinical safety

The safety profile of Eculizumab in the treatment of PNH is well characterised. The most commonly reported adverse reactions in eculizumab treated patients are headache, nasopharyngitis, nausea, pyrexia, myalgia, fatigue, and herpes simplex. Eculizumab treatment did not seem to be associated with an increase in severity of AEs in treated patients. No cumulative, irreversible toxicities have been reported.

Identified risks are general infections, especially meningococcal infections, which can be lifethreatening. Meningococcal sepsis, aspergillus infection, arthritis bacterial, upper respiratory tract infection, nasopharyngitis, bronchitis, oral Herpes, urinary tract infection and viral infection have been reported commonly in relation to eculizumab treatment. Prior to initiating Soliris therapy, it is recommended that PNH patients should receive immunizations according to current immunization guidelines. Additionally, all patients must be vaccinated against meningococcus at least 2 weeks prior to receiving Soliris. If available, tetravalent, conjugated vaccines are recommended. Due to its mechanism of action, Soliris therapy should be administered with caution to patients with active systemic infections. Soliris therapy shall not be initiated in patients with unresolved Neisseria meningitides infection, who are not currently vaccinated against Neisseria meningitides, or who have known or suspected hereditary complement deficiencies

Other commonly reported AEs include: dizziness, disgeusia, rash, alopecia, pruritus, arthralgia, myalgia, GI and respiratory symptoms and hypotension.

Other identified risks include haemolysis after drug discontinuation and haematologic abnormalities. Administration of Soliris may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis).

The risk of ADA is low. Infrequent, low titre antibody responses have been detected in Soliris treated patients across all PNH and non-PNH studies with a frequency (3.4%) similar to that of placebo (4.8%). No patients have been reported to develop neutralizing antibodies following therapy with Soliris, and there has been no observed correlation of antibody development to clinical response or adverse events.

No secondary tumours, other than transformation in CMML in a patient with MDS, were detected. Due to eculizumab's proposed mechanism of action, tumoural immunity is not expected to be affected in a major manner. There were no preclinical findings regarding this issue either. However, since limited long-term safety data are available and long term treatment is expected to be the rule, carcinogenic potential was keep in focus, particularly regarding haematological abnormalities.

Safety data from the SHEPHERD and TRIUMPH studies were included in the original MAA, approved in 2007. A subgroup analysis which included the 22 minimally transfused patients from the SHEPHERD study demonstrates consistency in the rates and severity of TEAEs and SAEs among patients who receive eculizumab, with and without a prior history of transfusion.

Safety data from the 144 patients in the no-eculizumab group and 45 patients in the eculizumab treated group with no history of transfusion from the PNH Registry were also presented. The analysis showed no substantive differences between the two groups. Five patients in the no-eculizumab patient group died and 1 death in the eculizumab-treated group was reported to the Pharmacovigilance database. No patients reported meningococcal infection. Overall these data are consistent with that known for this treatment and the PNH, and do not indicate any new safety findings.

Further, the safety profile of eculizumab in patients without a history of transfusion was consistent with previously reported safety updates and the current SmPC, however it should be noted that this was a small group of patients, i.e. 45 PNH patients. A low number of reports of targeted adverse events in the PNH Registry or TEAEs in the Alexion sponsored study (SHEPHERD) indicates no new safety concerns.

Overall analysis suggests that safety of eculizumab does not differ between PNH patients with or without a history of transfusion.

2.5.2. Conclusions on clinical safety

No new safety findings have been identified in the subset of patients with no history of transfusions exposed to eculizumab. No major differences would be expected in the safety profile when targeting a broader PNH population.

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

No revision to the RMP are deemed necessary as there is no new significant information regarding the safety specification, no additional pharmacovigilance activities nor further risk minimization activities required. The current version of eculizumab RMP (V10.1 submitted on March 12th, 2014) is acceptable.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

N/A

3. Benefit-Risk Balance

Benefits

Beneficial effects

A clinically relevant benefit can be seen following treatment with eculizumab independently of the prior history and burden of transfusions. The new main evidence comes from the PNH registry, concretely from a subset of 189 out of the 1547 patients included in the registry who fulfilled eligibility criteria: no history of transfusions, no prior treatment with eculizumab, LDH elevation, >1% granulocyte clone size, and at least 6-month FU. Of them, 45 started eculizumab treatment after inclusion while 144 did not received eculizumab. In the group treated with eculizumab a clinically meaningful decrease of LDH is observed (-1042 [-4215, 597]); An improvement of scores reflecting fatigue is observed (FACIT-fatigue score: +8 [-8; 32]; EORTC-fatigue score: -22[-67; 11]); An increase of hemoglobin level from 100 to 113 g/L is observed.

These data suggest that a treatment with eculizumab could improve the condition of the patients without recent history of transfusion and who present major signs of severity of PNH. Improvement in other related symptoms and a lower incidence of thrombotic events have been reported.

Supportive evidence from PNH with low and high transfusion requirements, from the studies submitted as part of the initial MA (Shepherd and Triumph), is presented for comparison.

Uncertainty in the knowledge-about the beneficial effects

Despite the pre-specified statistical analysis plan and the planned assessments every 6-month, there were a number of missing evaluations,; For LDH, 37 of 45 eculizumab treated nontransfused patients had values reported at 6 months follow-up. However there were a number of patients who did not complete the patient reported outcome assessments of FACIT-Fatigue and EORTC Fatigue. In addition, assessment was not blinded, which might have biased evaluation of subjective endpoints such that fatigue, dyspnoea, QoL, other related symptoms. The data have some limitations not unexpected from a Registry.

Given the differences in baseline disease characteristics between the two cohorts of patients within the Registry and those included in the Triumph and Shepherd Studies, a similar analysis of the benefits based on the endpoints used to support a positive benefit/risk balance cannot be made. Despite so, data presented are indicative of some symptomatic benefit as defined by the improvement in symptoms, QoL parameters and thrombotic events. The population included in the eculizumab cohort, based on the baseline disease characteristics, had more severe haemolysis with associated symptom and some experienced complications such as thrombotic events compared to those of the “no eculizumab” cohort. These findings indicate that a population of patients with PNH with haemolysis and clinical symptom(s) indicative of high disease activity might well benefit from treatment given the known associated morbidities.

Risks

Unfavourable effects

The safety profile of Eculizumab in the treatment of PNH is well characterised. The most commonly reported adverse reactions in eculizumab treated patients are headache, nasopharyngitis, nausea, pyrexia, myalgia, fatigue, and herpes simplex. Eculizumab treatment did not seem to be associated with an increase in severity of AEs in treated patients. No cumulative, irreversible toxicities have been reported.

Identified risks are general infections, especially meningococcal infections, which can be life threatening. Other commonly reported AEs include: dizziness, disgeusia, rash, alopecia, pruritus, arthralgia, myalgia, GI and respiratory symptoms and hypotension. Other identified risks include haemolysis after drug discontinuation and haematologic abnormalities. Administration of Soliris may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis).

Safety data from the SHEPHERD and TRIUMPH studies were included in the original MAA, approved in 2007. A subgroup analysis which included the 22 minimally transfused patients from the SHEPHERD study demonstrates consistency in the rates and severity of TEAEs and SAEs among patients who receive eculizumab, with and without a prior history of transfusion.

Safety data from the 144 patients in the no-eculizumab group and 45 patients in the eculizumab treated group with no history of transfusion from the PNH Registry were also presented. The analysis showed no substantive differences between the two groups. No patients reported meningococcal infection. Overall these data are consistent with what has been previously submitted and do not indicate any new safety findings. Limited top-line data suggest that safety of eculizumab does not differ between PNH patients with or without a history of transfusion.

Uncertainty in the knowledge about the unfavourable effects

As the unfavourable effects are well known already, no new uncertainties on the risks have been identified based on the new data provided.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Patients included in the Registry had not history of transfusions and based on the baseline disease characteristics it is considered this population represents a less severe population as compared to those of the Triumph Study but still a population with haemolysis and clinical symptoms indicative of high disease activity, which might well benefit from treatment given the known associated morbidities. Treatment with eculizumab provided a clinically relevant reduction in haemolysis and associated symptoms in those patients for whom data are available.

The safety profile of eculizumab is well characterised and in view of a clear clinical benefit it can be accepted with appropriate monitoring and clinical management.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

The benefit risk balance in the finally proposed indication, limited to patients with haemolysis and related clinical symptoms of high disease activity, regardless of transfusion history, reflects the studied population where data available support a positive benefit/risk balance.

4. Recommendations

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(s):

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	Type II

Extension of Indication to include paroxysmal nocturnal haemoglobinuria (PNH) where evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to correct some typographical errors in the product information.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include paroxysmal nocturnal haemoglobinuria (PNH) where evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to correct some typographical errors in the product information.

Summary

Please refer to the scientific discussion Soliris-H-C-791-II-66.