EU Risk Management Plan for Epysqli (eculizumab)

RMP version to be assessed as part of this application:

RMP version number: 2.0

Data lock point for this RMP: Nov 10, 2023

Date of final sign off: Nov 10, 2023

Rationale for submitting an updated RMP: To extend indication for the treatment of atypical hemolytic uremic syndrome (aHUS)

Summary of significant changes in this RMP:

1. To update the relevant sections applicable for the addition of the aHUS indication

Other RMP versions under evaluation: Not applicable

Details of the current approved RMP:

Version number: 1.2

Approved number with procedure: EMEA/H/C/006036/0000

Date of approval (opinion date): May 26, 2023

QPPV name: John Hart

The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

TABLE OF CONTENTS

TABLE OF CONTENTS **2**

LIST OF ABBREVIATIONS **5**

PART I: PRODUCT(S) OVERVIEW **6**

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S) **10**

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION **11**

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE **13**

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS **15**

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme **15**

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes **20**

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes **20**

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE **21**

SV.1 Post-authorisation exposure **21**

SV.1.1 Method used to calculate exposure 21

SV.1.2 Exposure 21

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION **22**

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS **23**

SVII.1 Identification of safety concerns in the initial RMP submission **23**

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP 23

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP 23

SVII.2 New safety concerns and reclassification with a submission of an updated RMP **23**

SVII.3 Details of important identified risks, important potential risks, and missing information **24**

SVII.3.1 Presentation of important identified risks and important potential risks 24

SVII.3.1.1 Important identified risk 24

SVII.3.1.2 Important potential risks 34

SVII.3.2 Presentation of the missing information 39

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS 40

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES) 41

III.1 Routine pharmacovigilance activities 41

III.2 Additional pharmacovigilance activities 41

III.3 Summary Table of additional Pharmacovigilance activities 41

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES 42

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES) 43

V.1. Routine Risk Minimisation Measures 43

V.2. Additional Risk Minimisation Measures 45

V.3 Summary of risk minimisation measures 49

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN 53

I. The medicine and what it is used for 53

II. Risks associated with the medicine and activities to minimise or further characterise the risks 53

II.A List of important risks and missing information 54

II.B Summary of important risks 54

II.B.1 Important identified risk 54

II.B.2 Important potential risk 58

II.B.3 Missing information 60

II.C Post-authorisation development plan 60

II.C.1 Studies which are conditions of the marketing authorisation 60

II.C.2 Other studies in post-authorisation development plan 60

PART VII: ANNEXES 61

Table of contents 61

Annex 1 – EudraVigilance Interface 62

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme 63

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan 64

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP 64

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP 64

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority 64

Annex 4 - Specific adverse drug reaction follow-up forms 65

Annex 5 - Protocols for proposed and on-going studies in RMP part IV 66

Annex 6 - Details of proposed additional risk minimisation activities 67

Annex 7 - Other supporting data (including referenced material) 69

Annex 8 – Summary of changes to the risk management plan over time 74

LIST OF ABBREVIATIONS

AA	Aplastic Anaemia
AE	Adverse Event
ADA	Anti-Drug Antibody
aHUS	Atypical haemolytic-uremic syndrome
C5	Complement component 5
CHO	Chinese Hamster Ovary
CI	Confidence Interval
DDD	Defined Daily Dose
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESRD	End Stage Renal Disease
EU	European Union
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
IBD	International Birth Date
Ig	Immunoglobulin
IP	Investigational product
IV	Intravenous
LDH	Lactate Dehydrogenase
MA	Marketing authorisation
MAA	Marketing Authorisation Applicant
mAb	monoclonal Antibody
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
PL	Package Leaflet
PNH	Paroxysmal Nocturnal Haemoglobinuria
PT	Preferred Term
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAF	Safety Set
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TMA	Thrombotic Microangiopathy
US	United States

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (International non-proprietary name or common name)	Eculizumab
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical Code)	Selective immunosuppressants (L04AA25)
Marketing Authorisation Applicant (MAA)	Samsung Bioepis NL B.V. (The Netherlands)
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	EPYSQLI 300 mg concentrate for solution for infusion
Marketing authorisation (MA) procedure	Centralised
Brief description of the product	Chemical class: EPYSQLI (eculizumab) is a recombinant humanised monoclonal Immunoglobulin (Ig) $G_{2/4k}$ antibody that binds to the human C5 complement protein and inhibits the activation of terminal complement. The eculizumab antibody contains human constant regions and murine complementarity-determining regions grafted onto the 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 Kilo-Dalton. Eculizumab is produced in a Chinese hamster ovary (CHO) cell line expression system and purified by affinity and ion exchange chromatography. The bulk drug substance manufacturing process also includes specific viral inactivation and removal steps.
	Mechanism of action: Eculizumab, the active ingredient in EPYSQLI, is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Eculizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes. In Paroxysmal nocturnal haemoglobinuria (PNH) patients, uncontrolled terminal complement activation and the resulting complement-mediated intravascular haemolysis are blocked with eculizumab treatment. In most PNH patients, eculizumab serum concentrations of approximately 35 microgram/mL are sufficient for essentially complete inhibition of terminal complement-mediated intravascular haemolysis. In PNH, chronic administration of eculizumab resulted in a rapid and sustained reduction in complement- mediated haemolytic activity. In aHUS patients, uncontrolled terminal complement activation and the

<table>
<tr><td></td><td>resulting complement-mediated thrombotic microangiopathy are blocked with eculizumab treatment. All patients treated with eculizumab when administered as recommended demonstrated rapid and sustained reduction in terminal complement activity.

In all aHUS patients, eculizumab serum concentrations of approximately 50 - 100 microgram/mL are sufficient for essentially complete inhibition of terminal complement activity.

In aHUS, chronic administration of eculizumab resulted in a rapid and sustained reduction in complement-mediated thrombotic microangiopathy.</td></tr>
<tr><td></td><td>Important information about its composition:

Eculizumab is a humanised monoclonal ($IgG_{2/4\kappa}$) antibody produced in CHO cell line by recombinant deoxyribonucleic acid technology.</td></tr>
<tr><td>Hyperlink to the Product Information</td><td>Product Information</td></tr>
<tr><td>Indication(s) in the EEA</td><td><u>Current:</u>

EPYSQLI is indicated in adults and children for the treatment of PNH</td></tr>
<tr><td></td><td><u>Proposed:</u>

EPYSQLI is indicated in adults and children for the treatment of PNH

and aHUS</td></tr>
<tr><td>Dosage in the EEA</td><td><u>Current:</u>

<u>Adult Patients in PNH:</u>

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

• Initial phase: 600 mg of EPYSQLI administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous (IV) infusion every week for the first 4 weeks.

• Maintenance phase: 900 mg of EPYSQLI administered via a 25 – 45 minute (35 minutes ± 10 minutes) IV infusion for the fifth week, followed by 900 mg of EPYSQLI administered via a 25 – 45 minute (35 minutes ± 10 minutes) IV infusion every 14 ± 2 days.

<u>Paediatric patients in PNH:</u>

Paediatric PNH patients with body weight ≥ 40 kg are treated with the adult dosing recommendations, respectively.

In paediatric PNH patients with body weight below 40 kg, EPYSQLI dosing regimen consists of:

<table>
<tr><th>Patient Body Weight</th><th>Initial Phase</th><th>Maintenance Phase</th></tr>
<tr><td>30 to <40 kg</td><td>600 mg weekly x 2</td><td>900 mg at week 3; then 900 mg every 2 weeks</td></tr>
<tr><td>20 to <30 kg</td><td>600 mg weekly x 2</td><td>600 mg at week 3; then 600</td></tr>
</table>
</td></tr>
</table>

		mg every 2 weeks
10 to <20 kg	600 mg weekly x 1	300 mg at week 2; then 300 mg every 2 weeks
5 to <10 kg	300 mg weekly x 1	300 mg at week 2; then 300 mg every 3 weeks

For more details on posology, please refer Summary of Product Characteristics (SmPC).

Proposed:

Adult Patients in PNH:

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

- Initial phase: 600 mg of EPYSQLI administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous (IV) infusion every week for the first 4 weeks.
- Maintenance phase: 900 mg of EPYSQLI administered via a 25 – 45 minute (35 minutes ± 10 minutes) IV infusion for the fifth week, followed by 900 mg of EPYSQLI administered via a 25 – 45 minute (35 minutes ± 10 minutes) IV infusion every 14 ± 2 days.

Paediatric patients in PNH:

Paediatric PNH patients with body weight ≥ 40 kg are treated with the adult dosing recommendations, respectively.

In paediatric PNH patients with body weight below 40 kg, EPYSQLI dosing regimen consists of:

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

For more details on posology, please refer Summary of Product Characteristics (SmPC).

atypical Haemolytic Uremic Syndrome (aHUS) in adults

The aHUS dosing regimen for adult patients (≥18 years of age) consists of a 4 week initial phase followed by a maintenance phase:

- Initial phase: 900 mg of Epysqli administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every week for the first 4 weeks.

<table>
<tr><td></td><td>
Maintenance phase: 1,200 mg of Epysqli administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion for the fifth week, followed by 1,200 mg of Soliris administered via a 25 – 45 minute (35 minutes ± 10 minutes) intravenous infusion every 14 ± 2 days.
Supplemental dosing of Epysqli is required in the setting of concomitant plasmapheresis (PP), plasma exchange (PE), or fresh frozen plasma infusion (PI) as described below:
<table>
<tr><th>Type of plasma intervention</th><th>Most recent Epysqli dose</th><th>Supplemental Epysqli dose with each PP/PE/PI Intervention</th><th>Timing of supplemental Epysqli dose</th></tr>
<tr><td rowspan="2">Plasmapheresis or plasma exchange</td><td>300 mg</td><td>300 mg per each plasmapheresis or plasma exchange session</td><td rowspan="2">Within 60 minutes after each plasmapheresis or plasma exchange</td></tr>
<tr><td>≥ 600 mg</td><td>600 mg per each plasmapheresis or plasma exchange session</td></tr>
<tr><td>Fresh frozen plasma infusion</td><td>≥ 300 mg</td><td>300 mg per infusion of fresh frozen plasma</td><td>60 minutes prior to each infusion of fresh frozen plasma</td></tr>
</table>
</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>
<u>Current:</u>
Concentrate for solution for infusion.
Clear, colourless, pH 7.0 solution.
One vial of 30 mL contains 300 mg of eculizumab (10 mg/mL).
After dilution, the final concentration of the solution to be infused is 5 mg/mL.

<u>Proposed:</u>
Not applicable
</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the European Union (EU)?</td><td>Yes</td></tr>
</table>

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

This module is not required for a biosimilar in accordance with Good Pharmacovigilance Practices (GVP) Module V – Risk management systems Table V.5., Summary of minimum RMP requirements for initial MA applications [GVP Module V].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

As outlined in the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" [EMA, 2012], a risk-based approach was taken to the non-clinical evaluation of EPYSQLI. A series of *in vitro* biologic activity studies were performed to demonstrate similarity between EPYSQLI and Soliris® and there were no significantly different results between EPYSQLI and Soliris®.

The *in vivo* non-clinical study was not performed since the *in vivo* pharmacodynamic (PD) study in irrelevant animal species is unlikely to provide any additional meaningful non-clinical evidence to demonstrate similarity between the EPYSQLI and Soliris®. It is acknowledged that eculizumab is highly species-specific with no appreciable activity against any other mammalian species [EMA Soliris®]. In addition, the identified epitope indeed includes the residue W917, which is unique for human C5 [Volk, 2016]. Of note, animal studies are less sensitive to detect differences between biosimilar and reference products and species differences between animals and humans limit the suitability of this approach to evaluate biosimilarity [Van Aerts, 2014]. Thus, *in vivo* animal studies, including pharmacology, pharmacokinetics (PK) and toxicology studies for EPYSQLI development were not performed and this was also endorsed by the European Medicines Agency (EMA) [EMA/CHMP/SAWP/634958/2017].

Although EPYSQLI had not been evaluated in a clinical setting prior to performance of this current study, *in vitro* biologic activity studies showed no significant differences of EPYSQLI compared to Soliris®. Based on the *in vitro* results, it was expected that EPYSQLI will exhibit similar clinical profiles compared to Soliris® and this Phase I study was designed to evaluate eculizumab profiles in healthy subjects at the dose of 300 mg.

Table SII.1: Summary of key safety findings from non-clinical studies

Toxicity	Rationale for not applicable
Single-dose Toxicity	No single-dose toxicity studies have been performed in accordance with the EMA guideline "*Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues*" [EMA/CHMP/BMWP/403543/2010] and the recommendations from the EMA [EMA/CHMP/SAWP/634958/2017] [SB12 NCO Section 2.4].
Repeat-dose Toxicity	No repeat-dose toxicity studies have been performed in accordance with the EMA guideline. "*Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues*" [EMA/CHMP/BMWP/403543/2010] [SB12 NCO Section 2.4].
Genotoxicity	No genotoxicity studies have been performed in line with the EMA guideline "*Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues*" [EMA/CHMP/BMWP/403543/2010] [SB12 NCO Section 2.4].
Carcinogenicity	No carcinogenicity studies have been performed in line with the EMA guideline "*Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues*" [EMA/CHMP/BMWP/403543/2010] [SB12 NCO Section 2.4].
Reproductive and Developmental	No reproductive and developmental toxicity studies have been performed in line with the EMA guideline "*Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues*"

Toxicity	Rationale for not applicable
Toxicity	[EMA/CHMP/BMWP/403543/2010] and the recommendations from the EMA [EMA/CHMP/SAWP/634958/2017] [SB12 NCO Section 2.4].
Local Tolerance	No local tolerance studies have been performed in line with the EMA guideline "*Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues*" [EMA/CHMP/BMWP/403543/2010] and the recommendations from the EMA [EMA/CHMP/SAWP/634958/2017] [SB12 NCO Section 2.4].
Other Toxicity Studies	Other toxicity studies (i.e. immunotoxicity) were not performed in line with the EMA guideline "*Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues*" [EMA/CHMP/BMWP/403543/2010] and the recommendations from the EMA [EMA/CHMP/SAWP/634958/2017] [SB12 NCO Section 2.4]. Since EPYSQLI is being developed as a biosimilar product to the reference product Soliris®, no additional non-clinical data are considered necessary.
Safety pharmacology	Safety pharmacology studies were not performed in line with the Scientific Advice with the EMA [EMA/CHMP/SAWP/634958/2017] and advice from the EMA guideline "*Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues*" [EMA/CHMP/BMWP/403543/2010]. Since EPYSQLI has been developed as a biosimilar to Soliris®, the safety pharmacology package developed for Soliris® should be considered when considering this type of toxicity [SB12 NCO Section 2.4]. As *in vivo* non-clinical toxicity study was not performed, there is no discussion nor conclusion to be made.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Safety data of EPYSQLI (eculizumab) are available from two clinical studies:

- SB12-1001- A randomised, double-blind, three-arm, parallel group, single-dose study to compare the PKs, safety, tolerability, immunogenicity, and PDs of eculizumab (SB12, EU sourced Soliris®, and United States (US) sourced Soliris®) in healthy subjects.
- SB12-3003- A randomized, double-blind, multicenter study, cross-over study to compare and evaluate the efficacy, safety, PK, and immunogenicity of SB12 compared to Soliris® in patients with PNH.

Exposure data from the two studies are presented separately. The data from the healthy volunteer study (SB12-1001) is summarised in the paragraphs below.

The clinical safety of SB12 has been assessed in two clinical studies, a clinical Phase I PK study in healthy subjects (SB12-1001) and a clinical Phase III efficacy and safety study in patients with PNH (SB12-3003). Safety of SB12 in these studies was assessed by monitoring adverse events (AEs), serious adverse events (SAEs), AEs special interest (e.g. *meningococcal* infection, other systemic infection, infusion-related reaction), vital signs, and laboratory evaluations as well as immunogenicity, which is an important safety aspect of therapeutic proteins.

In the clinical Phase I study SB12-1001, a total of 240 subjects were randomised to receive a single dose of eculizumab (a single dose of either SB12, EU Soliris®, or US Soliris® via IV infusion for 35 minutes) with 80 subjects in each three treatment groups (SB12, EU Soliris®, or US Soliris®), respectively. The Safety Set (SAF) consisted of all subjects who received investigational product (IP).

In the clinical Phase III study SB12-3003, a total of 50 patients were randomised to receive 600 mg of either SB12 or Soliris® IV infusion every week for the first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 2 weeks thereafter until Week 50. Patients who were randomised to initially receive SB12 were switched to receive Soliris® and patients who were randomised to initially receive Soliris® were switched to receive SB12 at Week 26. The SAF consisted of all patients who received at least one IP during the study period. As a result, a total of 49 patients were included in the SAF, with 25 (100.0%), 24 (96.0%), 16 (64.0%) and eight (32.0%) patients in the Soliris® to SB12, SB12 to All, SB12 to Soliris®, and Unplanned IP Switch (during Period 2, as comparator shortage occurred, a total of eight (16.0%) patients who were initially allocated in SB12 to Soliris® received SB12 instead of Soliris® to avoid abrupt discontinuation of eculizumab, based on the Sponsor assessment that treatment continuity for the patients should be of the highest importance) treatment sequences, respectively.

Exposure to SB12 in the Phase III clinical study SB12-3003 is summarised by duration of exposure in Table SIII. 1, by age group and gender in Table SIII. 2, and by ethnic or racial origin in Table SIII. 3. The total exposure from clinical trial for SB12 is approximately 23.444 patient-years (Table SIII. 1). Since all subjects received the same dose of SB12, exposure data is not represented based on dose. Special populations (e.g., pregnant women, lactating women, renal impairment, hepatic impairment, cardiac impairment, and immunocompromised) were excluded from the study and thus the exposure data was not represented for these populations.

Table SIII. 1: Duration of Exposure

Indication: PNH		
Duration of exposure	**Patients**	**SB12 exposure (patient-years)**
≥ 0 months	47	23.444
≥ 2 months	46	23.326
≥ 4 months	46	23.326
≥ 6 months	9	6.064
≥ 8 months	5	3.860
≥ 10 months	1	0.961
Total	**47**	**23.444**

Table SIII. 2: Age Group and Gender

Age group (years)	**Patients**		**SB12 exposure (patient-years)**	
	Male	**Female**	**Male**	**Female**
≤ 65	26	19	13.722	8.797
≥ 65	0	2	N/A	0.925
Total	**26**	**21**	**13.722**	**9.722**

Table SIII. 3: Ethnic Origin

Race	**Patients**		**SB12 exposure (patient-years)**	
	Male	**Female**	**Male**	**Female**
Asian	15	9	7.630	4.090
White	9	9	5.166	4.244
Other	2	3	0.925	1.388
Total	**26**	**21**	**13.722**	**9.722**

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

The clinical development programme for EPYSQLI as a biosimilar to Soliris® (eculizumab) comprised of two studies, Phase I study and a Phase III study. The first study was a randomised, double-blind, three-arm, parallel group, single-dose study to compare the PKs, safety, tolerability, immunogenicity, and PDs of eculizumab (SB12, EU sourced Soliris®, and US sourced Soliris®) in healthy subjects (study SB12-1001). The second study was a Phase III, randomised, double-blind, multicentre study to compare the efficacy, safety, PKs, and immunogenicity between SB12 (proposed eculizumab biosimilar) and Soliris® in subjects with PNH (study SB12-3003).

In the Phase I healthy volunteer study, inclusion and exclusion criteria were designed to ensure that the study population were healthy and homogenous to clarify any risks associated with the study and enable appropriate comparison of the PK, safety, tolerability, and immunogenicity of SB12 and Soliris®. Healthy female subjects of non-childbearing potential or healthy male subjects aged 18-55 years with all screening results within the normal range (or outside the normal range but not clinically significant) were included in the study.

Due to the concept and the nature of a phase I clinical study, the included or excluded population is not representative for a safety discussion on populations not studied in clinical trials, but for the discussion on the general safety.

In the Phase III study, inclusion and exclusion criteria were designed to compare the efficacy, safety, PKs, and immunogenicity between SB12 (proposed eculizumab biosimilar) and Soliris® in subjects with PNH. Male or female aged 18 or older and the mean age of all subjects was 38.1 years (range: 18-79 years) were enrolled in the study.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria described below are based on the Phase III study SB12-3003.

Table SIV.1.1: Had received previous treatment with a complement pathway inhibitor (including eculizumab)

Reason for exclusion	Previous treatments with complement pathway inhibitor can result in ADA responses in patients and these may also hamper interpretation of the efficacy or safety data thereby decreasing the sensitivity for detecting potential differences
Is it considered to be included as missing information?	No
Rationale	The information is included in the SmPC section 4.4 based on the information from the reference product. Since the SmPC are aligned to those of the reference product, the applicant does not consider the exclusion of these subpopulations to fulfil criteria of missing information.

Table SIV.1.2: Known hypersensitivity to the IP or any of the ingredients or excipients of the IP

Reason for exclusion	Administration of eculizumab may result in reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis).
Is it considered to be included as missing information?	No
Rationale	The Information is included in the SmPC section 4.3, 4.8 and Package Leaflet (PL) section 4. As stated in the SmPC and PL, hypersensitivity to SB12, murine proteins or to any of the excipients and ingredients are contraindicated, may affect up to 1 in 100 people.

Table SIV.1.3: Had a known contraindication/hypersensitivity for meningococcal vaccine or the antibiotic to be used in the study

Reason for exclusion	Based on the mechanism of action of eculizumab, use of it in patient results in susceptibility to increase meningococcal infection. Hence to reduce the risk, all patients must be vaccinated at least 2 weeks prior to receiving eculizumab. However, vaccination may not be sufficient to prevent *meningococcal* infection. So, consideration should also be given to the appropriate use of antibacterial agents.
Is it considered to be included as missing information?	No
Rationale	Patients who are with contraindication/hypersensitivity for *meningococcal* vaccine or the antibiotic to be used in the study cannot fulfil the criteria of vaccination because of chances of re-occurrence of hypersensitivity.

Table SIV.1.4: Had abnormal haematological parameters at screening defined as the following:

- **Absolute neutrophil count ≤ 0.5 × 10^3/µL**
- **Platelet count < 70 × 10^3/µL**

Reason for exclusion	Administration of eculizumab may result in abnormal haematological parameters such as leukopenia and thrombocytopenia.
Is it considered to be included as missing information?	No
Rationale	The information related to haematological abnormalities are included in the SmPC section 4.8.

Table SIV.1.5: Had a history of *meningococcal* disease

Reason for exclusion	The use of eculizumab increases the patient's susceptibility to meningococcal infection (*Neisseria meningitidis*).
Is it considered to be included as missing information?	No
Rationale	The information related to meningococcal disease is included in the SmPC section 4.3 based on the information from the reference product. Since the SmPC are aligned to those of the reference product, the applicant does not consider the exclusion of these subpopulations to fulfil criteria of missing information.

Table SIV.1.6: Had a history of haematopoietic stem cell transplantation

Reason for exclusion	Haematopoietic stem cell transplantation and eculizumab both constitute treatment options for PNH. Hence there can be hinderance of effectiveness of eculizumab in patients with history of haematopoietic stem cell transplantation.
Is it considered to be included as missing information?	No
Rationale	Exclude patient with pre-existing history of haematopoietic stem cell transplantation where eculizumab is unlikely to have an effect/effect is masked [de Fontbrune, 2015].

Table SIV.1.7: Had a history of serious thrombotic event (e.g., stroke, myocardial infarction, pulmonary embolism, etc.)

Reason for exclusion	Patients with history of serious thrombotic events will be on additional medications that can interact with eculizumab and could lead to morbidities which in turn can complicate the assessment of safety and effectiveness of the eculizumab.
Is it considered to be included as missing information?	No
Rationale	Excluding these patients reduces the risk of AEs caused by underlying conditions and reduces the difficulty in deciding whether an AE should be attributed to the pre-existing condition or to the eculizumab. At the same time, it eliminates the possibility of determining whether the drug has an adverse or beneficial effect in those populations.

Table SIV.1.8: Known or suspected active bacterial, virus, fungal infection within 30 days prior to initiation of study drug (Day 1)

Reason for exclusion	Treatment with eculizumab increases the risk of severe infections and sepsis.
Is it considered to be included as missing information?	No
Rationale	The information is included in the SmPC section 4.4 and 4.8 based on the information from the reference product. Since the SmPC are aligned to those of the reference product, the applicant does not consider the exclusion of these subpopulations to fulfil criteria of missing information.

Table SIV.1.9: Had a known history of human immunodeficiency (HIV) virus infection or had positive results at screening

Reason for exclusion	Due to complications related to immunosuppression in HIV patients, administration of eculizumab can increase the risk of infection. Eculizumab treatment may be associated with increased adverse effects for individuals with well controlled HIV infection.
Is it considered to be included as missing information?	No
Rationale	Excluded patient with history of HIV infection.

Table SIV.1.10: Concomitant use of any of the following medications is prohibited with the following conditions

- **Erythropoietin, systemic corticosteroids, low-molecular-weight heparins, iron supplements, and androgen therapy not on a stable dose for at least 4 weeks prior to initiation of study drug (Day 1)**
- **Warfarin with an unstable international normalised ratio for at least 4 weeks prior to initiation of study drug (Day 1) at the discretion of the Investigator**
- **Cyclosporine not on a stable dose for at least 8 weeks prior to initiation of study drug (Day 1)**

Reason for exclusion	Patients on concomitant medications can interact with eculizumab and could lead to morbidities which in turn can complicate the assessment of safety and effectiveness of the eculizumab. These drugs are also used as supportive therapy for PNH. Hence, they can influence the outcome of the study.
Is it considered to be included as missing information?	No
Rationale	Because of concerns about potential adverse impacts arising from concomitant medications.

Table SIV.1.11: Subjects who received or participated in another investigational drug, device, or

procedures within 30 days or within 5 half-lives of that IP prior to screening, whichever was greater

Reason for exclusion	It concerns about the elimination of the drug from the plasma. Drug interactions and the effects of the previous drug in the patient can be prevented by following the rationale of time frame.
Is it considered to be included as missing information?	No
Rationale	Time required for the concentration of a drug to fall to half of its initial concentration after reaching its peak is defined as half-live of a drug. 95-97% of the drug is eliminated after five half-lives. By this, interactions with the eculizumab and effects of the previous drug (therapeutic or adverse) can be prevented.

Table SIV.1.12: Had a history of malignancy within 5 years prior to screening, except for curatively treated carcinoma in situ of uterine cervix, basal cell carcinoma of the skin, or squamous cell carcinoma of the skin.

Reason for exclusion	These patients were excluded to provide better data quality.
Is it considered to be included as missing information?	No
Rationale	These patients were excluded to provide better data quality. The applicant does not suppose these exclusion criteria to have a sound basis for a deviation from the missing information described for the reference product.

Table SIV.1.13: Had any other cardiac, hepatic, immunologic, pulmonary, rheumatoid disease, other conditions causing rise in lactate dehydrogenase (LDH) (e.g., tumours, muscular dystrophies, liver and bile disease, etc.), or disorders which, at the discretion of the Investigator, would put the subjects at risk if enrolled.

Reason for exclusion	These conditions can lead to patients taking additional medications that can interact with an eculizumab, that could complicate the assessment of safety and effectiveness of the eculizumab. Excluding such patients reduces the risk of AEs caused by underlying conditions and reduces the difficulty in deciding whether an AE should be attributed to the pre-existing condition or to eculizumab.
Is it considered to be included as missing information?	No
Rationale	These are the conditions which can put the subject at risk. These can cause different effectiveness or safety responses to the eculizumab

Table SIV.1.14: Other unspecified reasons at the discretion of the Investigator or Sponsor, made the subjects unsuitable for enrolment.

Reason for exclusion	These includes comorbidities or concomitant treatment or factors that could mask the effect of the eculizumab. By these reasons there are chances of elimination of the possibility of determining whether eculizumab has an adverse or beneficial effect in PNH.
Is it considered to be included as missing information?	No
Rationale	These are the reasons which can influence safety and effectiveness of the eculizumab. Hence these reasons can characterise the patient and will be disqualified from participation.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3 presents an overview of special populations in the pre-authorization clinical development program.

Table SIV.3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programmes.
Breastfeeding women	Not included in the clinical development programmes.
Paediatric population	Not included in the clinical development programmes.
Elderly population	In the phase III clinical trial, elderly (≥ 65 years old) patients were included in the clinical development programmes. See details in Table SIII. 2.
Patients with relevant comorbidities: - Patients with hepatic impairment - Patients with renal impairment - Patients with cardiovascular impairment	Not included in the clinical development programmes.
Population with relevant different ethnic origin	In the phase III clinical trial, the majority of population were Asian (24 subjects), followed by White (18 subjects), and Other (5 subjects). See details in Table SIII. 3.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Epysqli sales data was obtained from local affiliates in the EU from the date of launch (Aug 11, 2023) to Sep 31, 2023. Epysqli had been marketed in a vial of 30ml containing 300 mg of eculizumab. Exposure was estimated using the WHO Defined Daily Dose (DDD) for eculizumab (64 mg/day), which is based on the dose given in the maintenance dose.

SV.1.2 Exposure

Cumulatively from the International Birth Date (IBD) through Sep 31, 2023, there were about 1.78 patient-years (PYs) of treatment for Epysqli.

Table SV.1: Exposure table by region

Region	Units Sold (Vial)	Estimated Exposure (Person-Years)
EU	139	1.78

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Given to the specific mechanism of action of eculizumab, no illegal use is to be expected.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

The risks are aligned with those of the reference product.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Based on the EMA guidance on similar biological medicinal products, the RMP should take into account the risks associated with the use of the reference product. The following risks are the safety concerns of both EPYSQLI and the reference product, Soliris®.

Important identified risks	Important potential risks	Missing information
• Meningococcal infections • Serious infections (including sepsis) • *Aspergillus* infection • Infusion reactions • Severe thrombotic microangiopathy (TMA) complications due to drug discontinuation in aHUS patients	• Serious haemolysis after drug discontinuation in PNH patients • Immunogenicity	None

Risk-benefit impact:

The above-included risks are considered important because they may lead to serious, even life-threatening events. They may also lead to discontinuation of therapy even if the AE is non-serious.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

New Important Identified Risks

- Severe TMA complications due to drug discontinuation in aHUS patients

Reason for addition: to align the safety concerns of the reference product due to the addition of aHUS indication

Removed Important Identified Risks

- Malignancies and haematologic abnormalities in PNH patients
- Serious infections in neonates after maternal exposure to eculizumab

Reason for removal: to align the safety concerns of the reference product

SVII.3 Details of important identified risks, important potential risks, and missing information

Based on the EMA guidance on similar biological medicinal products, the RMP should take into account identified and potential risks associated with the use of the reference product. Therefore, this section will contain all the important identified risks and important potential risks described in the RMP for the reference product, Soliris®, and from the scientific literature.

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 Important identified risk

Meningococcal infections

Potential mechanisms:

Eculizumab mode of action is based on terminal complement C5 inhibition. Deficiency of terminal complement components is associated with an increased incidence of infection with *Neisseria species*, in particular *N. meningitidis*.

Evidence source(s) and strength of evidence:

This identified risk is based on the results from the clinical development programme for eculizumab. Eculizumab mode of action is based on terminal complement C5 inhibition which is associated with an increased incidence of meningococcal infections caused by *N. meningitidis*, as *meningococcus* is primarily cleared by the terminal complement components.

Further evidence linking meningococcal infections to terminal complement inhibition can be found in the scientific literature [Figueroa, 1991; Ross, 1984; Balmer, 2002; Cartwright, 2001; Ram, 2010].

Characterisation of the risk:

Frequency with 95% Confidence Interval (CI):

No cases were reported in the EPYSQLI Phase III study.

Severity:

Meningococcal infection is usually serious in nature and can quickly become life-threatening or fatal if not recognised early and treated with appropriate antibiotics.

Cases of *meningococcal* infections have been reported in eculizumab-treated patients. All cases were considered as serious and all patients were hospitalised. The most severe patients required intensive care. Sepsis was the most frequent clinical presentation of the disease.

Reversibility and long-term outcomes:

Acute infection must be timely treated with antibiotics and patients usually recover after such treatment, although may be left with sequelae. Cases with fatal outcomes have been observed in the post-marketing setting.

Impact on quality of life:

Since *meningococcal* infections are usually serious and life-threatening infectious diseases with

potentially fatal outcomes, requiring hospitalisation and timely antibiotic treatment, the impact on patients' quality of life is significant. Moreover, patients may be left with sequelae such as neurological changes or amputations of fingers/toes.

Risk factors and risk groups:

Main risk factors for these infections include:

- Genetic deficiency or therapeutic inhibition of terminal complement
- Lack of commercially available vaccine against certain meningococcus serogroup
- (Partial) resistance of meningococcal strain to prophylactic antibiotics
- Professionals who are exposed to environments of greater risk for meningococcal disease
- Research, industrial, and clinical laboratory personnel who are routinely exposed to *N. meningitidis*
- Military personnel during recruit training (military personnel may be at increased risk of *meningococcal* infection when accommodated in close quarters)
- Day-care centre workers
- Living on a college or university campus
- Travelling to endemic areas for *meningococcal* meningitis (e.g. India, Sub-Saharan Africa, pilgrimage to Saudi Arabia for Hajj).

No data were identified as additional risk factors for *meningococcal* infections related to underlying disease such as PNH or aHUS.

Preventability:

The occurrence of *meningococcal* infections can be prevented in some cases by means of meningococcal vaccines. However, it is recognised that *meningococcal* vaccination may not prevent all cases of *meningococcal* infections.

Also, available meningococcal vaccines do not cover all serogroups. In patients who cannot receive meningococcal vaccine, including infants or patients at risk of developing further activation of their underlying complement mediated disease, antibiotic prophylaxis could prevent meningococcal infections.

Refer to Part V.2 for a detailed description of additional risk minimisation measures for EPYSQLI, designed to prevent and/or minimise this risk.

Impact on the risk-benefit balance of the product:

Meningococcal infections are life-threatening (and potentially fatal) conditions with significant impact on patient's quality of life (especially if presenting with sequelae), hence, the implementation of additional risk minimisation measures. The data available to date suggest a stable overall reporting rates of *meningococcal* infections in patients treated with eculizumab of 0.3 to 0.5 per 100 patient-years over the five past years with reported fatal outcomes similar to the reporting rate in the general population. The mitigation measures in place for the risk of *meningococcal* infections appear to be appropriate and effective.

Public health impact:

Meningococcal infections represent life-threatening diseases. The impact of these infections on patients can be minimised by early recognition of the symptoms by patients/healthcare professionals (HCPs), and early institution of appropriate antibiotics.

The post-marketing reporting rate of *meningococcal* infection in patient treated with eculizumab has continued to be consistent over the 10 years of post-marketing experience at approximately 0.3 to 0.5 per 100 patient-years over the past 5 years. The reporting rate for fatal outcome remained stable as well at 0.03 per 100 patient-years representing 9.2% of patients who experienced *meningococcal* infections, similar to the reporting rate in the general population (10% to 15%) [Rosenstein, 1999; van Deuren, 2000].

Serious infections (including sepsis)

Potential mechanisms:

Eculizumab mode of action is based on terminal complement C5 inhibition which is associated with an increased incidence of neisserial infections, as *Neisseria spp*. are primarily cleared by terminal complement components. The role of terminal complement inhibition in incidence of other serious infections is much lower as eculizumab does not inhibit early complement components which are able to clear most of infections other than those caused by *Neisseria spp*.

Evidence source(s) and strength of evidence:

This identified risk is based on the results from the clinical development programme for eculizumab. Eculizumab mode of action is based on terminal complement C5 inhibition, impacting in a minor way the ability to clear also infections other than *Neisseria spp.* infections in eculizumab-treated patients, potentially leading to serious infections and/or sepsis, even though this impact is significantly lower since early complement components are not affected by eculizumab.

However, scientific literature shows that patients with terminal complement deficiency are only at increased risk of *Neisseria spp*. infections [Figueroa, 1991; Ram, 2010] same as data from PNH registry of the originator (Soliris®) comparing treated and untreated patients which do not demonstrate association between eculizumab treatment and infections other than *Neisseria spp*. infections.

Characterisation of the risk:

Frequency with 95% CI:

There was one serious event of serious infections (including sepsis) in one patient treated with EPYSQLI (subject incidence: 2.128%; 95% CI: 0.054, 11.294) corresponding to an exposure-adjusted event rate of 4.265 events per 100 patient-years (95% CI: 0.108, 23.766). There was one serious event of serious infections (including sepsis) in one patient treated with Soliris® (subject incidence: 2.128%; 95% CI: 0.054, 11.294) corresponding to an exposure-adjusted event rate of 5.096 events per 100 patient-years (95% CI: 0.129, 28.395).

Table SVII.3.1.1.1: Subject incidence and exposure-adjusted rate of serious infections TEAEs from the Phase III Study

Actual Treatment	Total subject N	No. of subjects with event N1 (%)a	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rateb	Exp-adj rate 95% CI
EPYSQLI	47	1 (2.128)	0.054, 11.294	23.444	1	4.265	0.108, 23.766

Actual Treatment	Total subject N	No. of subjects with event N1 (%)a	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rateb	Exp-adj rate 95% CI
Soliris®	47	1 (2.128)	0.054, 11.294	19.622	1	5.096	0.129, 28.395

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Number and frequency of serious infections TEAEs from the Phase III Study

MedDRA PT	EPYSQLI N = 47	Soliris® N = 47
	n	n
Cellulitis	0	1
Wound infection bacterial	1	0

N = Total subjects; n = No. of subjects with events

Seriousness/outcomes:

There was one serious event of serious infections (including sepsis) in one patient treated with EPYSQLI (subject incidence: 2.128%; 95% CI: 0.054, 11.294) corresponding to an exposure-adjusted event rate of 4.265 events per 100 patient-years (95% CI: 0.108, 23.766). There was one serious event of serious infections (including sepsis) in one patient treated with Soliris® (subject incidence: 2.128%; 95% CI: 0.054, 11.294) corresponding to an exposure-adjusted event rate of 5.096 events per 100 patient-years (95% CI: 0.129, 28.395).

Table SVII.3.1.1.2: Subject incidence and exposure-adjusted rate of serious infections TEAEs that were serious from the Phase III Study

Actual Treatment	Total subject N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rate[b]	Exp-adj rate 95% CI
EPYSQLI	47	1 (2.128)	0.054, 11.294	23.444	1	4.265	0.108, 23.766
Soliris®	47	1 (2.128)	0.054, 11.294	19.622	1	5.096	0.129, 28.395

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Severity:

Infections may become rapidly serious in immunocompromised patients such as patient with bone marrow disorders, renal failure or receiving immunosuppressive drugs. Serious infections have been reported in patients receiving eculizumab. Patients generally recovered without sequelae after anti-infective treatment.

Most of these reports were confounded by other underlying severe conditions known as risk factors for serious infection such as bone marrow failure, renal failure with dialysis, Diabetes Mellitus or concomitant immunosuppressive therapy.

The severity of serious infections range from mild to severe. Serious infection does represent a severe condition with a potential for fatal outcome. Sepsis is usually serious and can quickly become life-threatening or fatal if not recognised early and treated appropriately.

In the EPYSQLI treatment group, one event of serious infections (including sepsis) was reported to be

severe in severity (4.265 events per 100 patient-years; 95% CI: 0.108, 23.766). In the Soliris® treatment group, one event of serious infections (including sepsis) was reported to be severe in severity (5.096 events per 100 patient-years; 95% CI: 0.129, 28.395).

Table SVII.3.1.1.3: Subject incidence and exposure-adjusted rate of serious infections TEAEs that were severe from the Phase III Study

Actual Treatment	Total subject N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rate[b]	Exp-adj rate 95% CI
EPYSQLI	47	1 (2.128)	0.054, 11.294	23.444	1	4.265	0.108, 23.766
Soliris®	47	1 (2.128)	0.05, 11.294	19.622	1	5.096	0.129, 28.395

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Reversibility and long-term outcomes:

Reversibility and long-term outcomes depend on the nature of infection and characteristics of affected patient. The experience from the clinical trials with eculizumab shows that patients who developed serious infection generally recovered without sequelae with appropriate antibiotic treatment. However, cases of sepsis (mostly associated with *meningococcal* infections) with fatal outcomes have been reported.

In a study, seven children (median age 12 months, range 3-28 months) diagnosed with Post-transplant haemolytic uremic syndrome, out of which three patients were treated with the complement C5 inhibitor eculizumab. During a median follow-up time of 11.3 years, one patient died due to infectious complications after transplantation [Holle, 2021].

Impact on quality of life:

Sepsis is a systemic response to an acute infection. For patients who experience infection or sepsis, the impact on quality of life is significant due to prolonged hospitalisation for antibiotic therapy and supportive care.

Risk factors and risk groups:

Underlying immunodeficiency condition represents general risk factor for serious infection: either acquired (e.g. Aplastic Anaemia (AA) or Myelodysplastic Syndromes (MDS) in patients with PNH or End Stage Renal Disease (ESRD) in patients with aHUS) or due to immunosuppressive drugs.

Preventability:

Increased awareness of HCP and patient about the risk of infection and the related signs and symptoms of serious infection are helpful in minimising the impact of the risk. Eculizumab should be administered with caution to patients with active systemic infections. Prior to initiating eculizumab, it is recommended that patients should initiate immunisations according to current immunisation guidelines.

All patients must be vaccinated against *meningococcal* infections at least 2 weeks prior to receiving EPYSQLI unless the risk of delaying EPYSQLI therapy outweighs the risks of developing a *meningococcal* infection. Patients who initiate EPYSQLI treatment less than 2 weeks after receiving a *meningococcal* vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients less than 18 years of age must be vaccinated against Haemophilus influenzae

and pneumococcal infections, and strictly need to adhere to the national vaccination recommendations for each age group.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases, including PNH, may experience increased signs and symptoms of their underlying disease, such as haemolysis (PNH). Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

Refer to Part V.2 for a detailed description of additional risk minimisation measures for EPYSQLI, designed to prevent and/or minimise this risk.

Impact on the risk-benefit balance of the product:

Since this risk is directly associated with the mechanism of eculizumab action, it has a significant impact on the benefit-risk balance of EPYSQLI, but acceptable in the light of the anticipated benefits of the therapy. The reported rate of serious infections including sepsis remained stable over the 10 years of post-marketing experience with EPYSQLI. Risk minimisation measures in place and long-term post-marketing experience with eculizumab showed that all patients who experienced serious non-*meningococcal* infections were noted to have severe underlying conditions with associated immunosuppressive treatment and co-morbidities.

Public health impact:

Serious infections could be life-threatening or fatal. Generally, serious infections require prolonged. hospitalisation for antibiotic therapy and supportive care. Close monitoring of serious infections including sepsis over the 10 years of post-marketing experience demonstrates no significant increase of serious infections other than infections with *Neisseria spp*. in patients treated with eculizumab. In addition, data from PNH registry of the originator (Soliris®) comparing treated and untreated patients do not demonstrate association between eculizumab treatment and infections other than *Neisseria* infections.

Aspergillus infection

Potential mechanism(s):

Host defence against *Aspergillus* infection is mainly driven by cellular immunity and complement component (C3a, C3b iC3b, and C5a) allowing chemotaxis and opsonisation, thus eculizumab C5 blockade has only a partial effect on host defence against *Aspergillus* infections.

Evidence source(s) and strength of evidence:

This identified risk is based on the results from the clinical development programme for eculizumab for prevention of antibody mediated rejection in kidney transplant recipients (Study C10-001 and C10-002). Since host defence against *Aspergillus* infection is mainly driven by cellular immunity and complement component (C3a, C3b iC3b, and C5a), allowing chemotactism and opsonisation, eculizumab C5 blockade has only a partial effect on the host defence against *Aspergillus* infections and therefore, has been observed only in severely immunocompromised patients. Further evidence linking *aspergillosis* to immunocompromised states is provided in the scientific literature [Speth, 2012; Lin, 2001; Galimberti, 2012; Valdez, 2009; Weinberger, 1992; Ruhnke, 2007; Rüping, 2008].

Characterisation of the risk:

Frequency with 95% CI:

No cases were reported in the EPYSQLI Phase III study.

Severity:

Aspergillus infection, particularly invasive *aspergillosis* is usually serious and can quickly become life-threatening or fatal if not recognised early and treated appropriately.

Aspergillus infections and particularly invasive *aspergillosis* does represent a severe condition with a potential for fatal outcome.

Reversibility and long-term outcomes:

Despite antimycotic therapy and surgical interventions, the fatality of invasive *aspergillosi*s is high and depends on the degree of immunosuppression and on the affected organs.

In the prospective cohort study, patients were treated with eculizumab after transplantation were divided into the therapeutic (onset of aHUS after transplantation) and prophylactic use (patients with previous diagnosis of aHUS undergoing kidney transplantation). In this study one patient died at six months, due to *Aspergillus* infection [de Andrade, 2017].

Impact on quality of life:

Aspergillus infection is an acute infection with potentially significant impact on affected patients.

Risk factors and risk groups:

Underlying severe immunodeficiency condition, acquired or due to other immunosuppressive drugs including steroids, exposure to construction or demolition, severe pancytopenia due to aplastic anaemia (AA), and pre-existing lung impairment or pre-existing *Aspergillus* infection.

Preventability:

Increased awareness of HCP and patient about the risk of *Aspergillus* infection and underlying risk factors to develop an *Aspergillus* infection are helpful in minimising the impact of the risk.

Eculizumab should be administered with caution to patients with active systemic infections, including *Aspergillus* infections. Consider the risk factors to develop an *Aspergillus* infection prior starting treatment with eculizumab and take appropriate measures to mitigate the risk. Refer to Part V.2 for a detailed description of additional risk minimisation measures for EPYSQLI, designed to prevent and/or minimise this risk.

Impact on the risk-benefit balance of the product:

Aspergillus infections are life-threatening condition with potentially fatal outcomes. hence, the implementation of risk minimisation measures. The reporting rates from post-marketing *Aspergillus* infections in patients treated with eculizumab have been stable over the past 5 years and similar to the rates in patients at risk (i.e. severely immunosuppressed individuals) within the general population.

Public health impact:

Invasive *Aspergillus* infection is a life-threatening infection which can be fatal. Early recognition and treatment is important in mitigating the risk. The reporting rate for post-marketing *Aspergillus* infections has been stable over the past 10 years and when documented, all cases include multiple confounding factors severe immunosuppression in particular that provide alternative causal association. Patient treated with eculizumab appears to have similar reporting rate as patients at-risk within the general population. No difference in occurrence of *Aspergillus* infections has been observed in PNH registry of the originator (Soliris®) when comparing treated and non-treated patients.

Infusion reactions

Potential mechanism(s):

As with all therapeutic proteins, administration of EPYSQLI may result in infusion reactions and could cause allergic or hypersensitivity reactions.

Evidence source(s) and strength of evidence:

This identified risk is based on the observations made within the clinical development programme for eculizumab. As with all therapeutic proteins, administration of EPYSQLI may result in infusion reactions and could cause allergic or hypersensitivity reactions. Most of infusion-reactions which occurred in patients receiving eculizumab were non-serious and did not required discontinuation of eculizumab. In the post marketing setting anaphylactic / anaphylactoid reactions have been reported during or following eculizumab infusion.

In PNH clinical studies, AEs were documented in the case report form as to whether they occurred within 24 or 48 hours of study medication.

Characterisation of the risk:

Frequency with 95% CI:

There were three events of infusion reactions in three patients treated with EPYSQLI (subject incidence: 6.383%; 95% CI: 1.336, 17.539) corresponding to an exposure-adjusted event rate of 12.796 events per 100 patient-years (95% CI: 2.639, 37.396). There were 13 events of infusion reactions in 11 patients treated with Soliris® (subject incidence: 23.404%; 95% CI: 12.303, 38.026), and the corresponding exposure-adjusted event rate was 66.252 events per 100 patient-years (95% CI: 35.276, 113.292).

Table SVII.3.1.1.4 Incidence and exposure-adjusted rate of infusion reactions TEAEs from the Phase III Study

Actual Treatment	Total subject N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rate[b]	Exp-adj rate 95% CI
EPYSQLI	47	3 (6.383)	1.336, 17.539	23.444	3	12.796	2.639, 37.396
Soliris®	47	11 (23.404)	12.303, 38.026	19.622	13	66.252	35.276, 113.292

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Number and frequency of infusion reactions TEAEs from the Phase III Study

MedDRA PT	EPYSQLI N = 47	Soliris® N = 47
	n	n
Allergic transfusion reaction	0	1
Dermatitis acneiform	0	1
Dermatitis allergic	1	1
Dermatitis atopic	0	1
Eczema	1	1
Erythema nodosum	0	1
Infusion site hypersensitivity	0	1
Mouth ulceration	0	1
Rash	0	2

MedDRA PT	EPYSQLI N = 47	Soliris® N = 47
	n	n
Rash erythematous	0	1
Rhinitis allergic	0	1
Urticaria	1	1

N = Total subjects; n = No. of subjects with events

Seriousness/outcomes:

There were no events of serious infusion reactions after drug discontinuation in patients treated with EPYSQLI. There was one event of serious infusion reactions in one patient treated with Soliris® (subject incidence: 2.128%; 95% CI: 0.054, 11.294) corresponding to an exposure-adjusted event rate of 5.096 events per 100 patient-years (95% CI: 0.129, 28.395).

Table SVII.3.1.1.5: Incidence and exposure-adjusted rate of infusion reactions TEAEs that were serious from the Phase III Study

Actual Treatment	Total subject N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rate[b]	Exp-adj rate 95% CI
EPYSQLI	47	0	N/A	0	0	0	0
Soliris®	47	1 (2.128)	0.054, 11.294	19.622	1	5.096	0.129, 28.395

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Severity:

There were no severe events of infusion reactions in patients treated with EPYSQLI. In the Soliris® treatment group, one event of infusion reactions was reported to be severe in severity (5.096 events per 100 patient-years; 95% CI: 0.129, 28.395).

Table SVII.3.1.1.6: Incidence and exposure-adjusted rate of infusion reactions TEAEs that were severe from the Phase III Study

Actual Treatment	Total subject N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rate[b]	Exp-adj rate 95% CI
EPYSQLI	47	0	N/A	0	0	0	0
Soliris®	47	1 (2.128)	0.054, 11.294	19.622	1	5.096	0.129, 28.395

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Reversibility:

Infusion reactions are fully reversible if recognised early and treated in a timely manner by appropriate measures.

Long-term outcomes:

None expected

Impact on quality of life:

None

Risk factors and risk groups:

Patients with hypersensitivity to eculizumab, murine proteins or to any of the excipients. No data were identified for the risk factors for infusion reactions in patients with PNH.

Preventability:

Do not initiate EPYSQLI therapy in patients with known hypersensitivity to eculizumab, murine proteins or to any of the excipients.

Refer to Part V.2 for a detailed description of additional risk minimisation measures for EPYSQLI, designed to prevent and/or minimise this risk.

Impact on the risk-benefit balance of the product:

The impact of this risk on benefit-risk profile of EPYSQLI is acceptable in the light of the anticipated benefits of the therapy and risk minimisation measures in place.

Public health impact:

Administration of eculizumab may result in infusion reactions. Infusion reactions are usually benign and consist of redness, pruritus, local pain. In rare instances, infusion reactions may lead to very severe complications such as anaphylactic shock.

Due to the low frequency of serious infusion reactions, limited impact on public health is expected for this important identified risk.

Severe TMA complications due to drug discontinuation in aHUS patients

Potential mechanism(s):

aHUS is a chronic and debilitating life-threatening disease due to life-long uncontrolled complement activation. Eculizumab treatment inhibits this otherwise uncontrolled complement activation. The discontinuation of eculizumab can result in signs and symptoms of severe TMA complications.

Evidence source(s) and strength of evidence:

This risk resulted from the clinical development programme for eculizumab in aHUS patients. aHUS is a chronic and debilitating life-threatening disease due to life-long uncontrolled complement activation. Eculizumab treatment inhibits this otherwise uncontrolled complement activation. The discontinuation of eculizumab can result in signs and symptoms of severe TMA complications. The efficacy results from C11-003 observational study indicate that patients who discontinued eculizumab experience a higher rate of TMA complications (3-fold) compared to patients who never discontinued eculizumab treatment.

Characterisation of the risk:

Frequency with 95% CI:

No study was conducted for aHUS patients with EPYSQLI.

Seriousness/outcomes:

No study was conducted for aHUS patients with EPYSQLI.

Severity:

No study was conducted for aHUS patients with EPYSQLI.

Reversibility:

If aHUS patients discontinue treatment with Epysqli, they should be monitored closely for signs and symptoms of severe TMA complications. Monitoring may be insufficient to predict or prevent severe thrombotic microangiopathy complications in patients with aHUS after discontinuation of Epysqli.

Long-term outcomes:

ESRD in kidney allograft requiring chronic dialysis; ESRD; residual renal insufficiency, kidney transplant patients

Impact on quality of life:

Severe TMA complications could be triggered by eculizumab discontinuation and may lead to kidney failure or ESRD. Providing that the patients are normally receiving eculizumab to treat their condition there is no impact on patient's quality of life.

Risk factors and risk groups:

Complement dysregulation due to genetic abnormalities or acquired deficiencies in patients with aHUS is associated with TMA [Tsai 2006, Benz and Amann 2010].

Preventability:

Increased awareness of HCP and patient about the risk of TMA complications after discontinuation and their related signs and symptoms are helpful in minimising the impact of the risk.

Refer to Part V.2 for a detailed description of additional risk minimisation measures for Epysqli, designed to prevent and/or minimise this risk.

Impact on the risk-benefit balance of the product:

The impact of this risk on benefit-risk profile of EPYSQLI is acceptable in the light of the anticipated benefits of the therapy and risk minimisation measures in place.

Public health impact:

Severe TMA complications are associated with life-threatening conditions including acute renal failure potentially leading to ESRD requiring chronic dialysis and/or renal transplant. Other manifestations of severe TMA complications can affect multiple organs such as lung, heart, brain and lead to devastating complications.

Patients and HCPs are provided with educational materials to inform them of this risk and provide means to mitigate and address this risk by identifying signs/symptoms and procedures/treatments in case of severe TMA complications. These educational materials recommend patients to be closely monitored at least 12 weeks after Epysqli discontinuation.

SVII.3.1.2 Important potential risks

Serious haemolysis after drug discontinuation in PNH patients

Potential mechanism (s):

Patients with PNH experience chronic haemolysis of terminal complement inhibitor deficient red blood cells. To the extent that eculizumab effectively prevents lysis of these cells, the PNH red blood cells may become a higher proportion of the red blood cell population with eculizumab treatment.

Therefore, PNH patients treated with eculizumab for a period long enough to increase their number of PNH red blood cells are potentially at risk for serious haemolysis following discontinuation of eculizumab therapy.

Evidence source(s) and strength of evidence:

This potential risk is a theoretical possibility in PNH patients, based on the mode of eculizumab action and nature of PNH.

Characterisation of the risk:

Frequency with 95% CI:

There were two events of serious haemolysis post discontinuation in two patients treated with EPYSQLI (subject incidence: 4.255%; 95% CI: 0.520, 14.541) corresponding to an exposure-adjusted event rate of 8.531 events per 100 patient-years (95% CI: 1.033, 30.817). There were no events of serious haemolysis post discontinuation in patients treated with Soliris®.

Table SVII.3.1.1.7: Incidence and exposure-adjusted rate of serious haemolysis after drug discontinuation TEAEs from the Phase III Study

Actual Treatment	Total subject N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rate[b]	Exp-adj rate 95% CI
EPYSQLI	47	2 (4.255)	0.520, 14.541	23.444	2	8.531	1.033, 30.817
Soliris®	47	0	N/A	0	0	0	0

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Number and frequency of Serious haemolysis after drug discontinuation in PNH patients TEAEs from the Phase III Study

MedDRA PT	EPYSQLI N = 47	Soliris® N = 47
	n	n
Haemolysis	2	0

N = Total subjects; n = No. of subjects with events

Seriousness/outcomes:

There was one event of serious haemolysis post discontinuation in one patient treated with EPYSQLI (subject incidence: 2.128%; 95% CI: 0.054, 11.294) corresponding to an exposure-adjusted event rate of 4.265 events per 100 patient-years (95% CI: 0.108, 23.766). There were no events of serious haemolysis post discontinuation in patients treated with Soliris®.

Table SVII.3.1.1.8: Incidence and exposure-adjusted rate of serious haemolysis after drug discontinuation TEAEs that were serious from the Phase III Study

Actual Treatment	Total subject N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rate[b]	Exp-adj rate 95% CI
EPYSQLI	47	1 (2.128)	0.054, 11.294	23.444	1	4.265	0.108, 23.766

Soliris®	47	0	N/A	0	0	0	0

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Severity:

In the EPYSQLI treatment group, one event of serious haemolysis post discontinuation was reported to be severe in severity (4.265 events per 100 patient-years; 95% CI: 0.108, 23.766). There were no severe events of serious haemolysis after drug discontinuation in patients treated with Soliris®.

Serious haemolysis post discontinuation of EPYSQLI is defined as serum lactate dehydrogenase levels greater than the pre-treatment level, along with any of the following: greater than 25% absolute decrease in PNH clone size (in the absence of dilution due to transfusion) in one week or less, a haemoglobin level of <5g/dL or a decrease of >4g/dL in one week or less, angina, change in mental status, a 50% increase in serum creatinine level, or thrombosis.

Table SVII.3.1.1.9: Incidence and exposure-adjusted rate of serious haemolysis after drug discontinuation TEAEs that were severe from the Phase III Study

Actual Treatment	Total subject N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rate[b]	Exp-adj rate 95% CI
EPYSQLI	47	1 (2.128)	0.054, 11.294	23.444	1	4.265	0.108, 23.766
Soliris®	47	0	N/A	0	0	0	0

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Reversibility:

These effects can be reversed by re-initiation of EPYSQLI therapy. No other measures have yet been established.

Long-term outcomes:

Not yet established

Impact on quality of life:

Aggravation of serious haemolysis may occur because of eculizumab discontinuation and it may profoundly impact patient's quality of life. Providing that the patients are normally receiving eculizumab to treat their condition, there is no impact on patient's quality of life.

Risk factors and risk groups:

PNH: No data were identified for risk factors for serious haemolysis due to drug discontinuation in patients with PNH.

Preventability:

Not preventable

Refer to Part V.2 for a detailed description of additional risk minimisation measures for EPYSQLI, designed to minimise this risk.

Impact on the risk-benefit balance of the product:

This potential risk is based on the theoretical possibility, associated with abrupt drug discontinuation, resulting in a so-called rebound effect. Rebound effect is described for many biologicals but has not yet been observed with eculizumab. The potential impact of this risk on benefit-risk balance of EPYSQLI is considered acceptable in the light of anticipate benefits of the therapy.

Public health impact:

Serious haemolysis following discontinuation of eculizumab therapy may lead to severe complications such as anaemia, angina, change in mental status, creatinine increase or thrombosis.

Educational materials recommend the patient to be closely monitored up to eight weeks after EPYSQLI discontinuation.

Considering the ultra-rare nature of PNH, no significant impact on public health is expected.

Immunogenicity

Potential mechanism(s):

Even though immunogenicity is a known class effect of monoclonal antibody (mAb), it has not been demonstrated with eculizumab.

Evidence source(s) and strength of evidence:

This potential risk is based on the known potential of all medicinal products and on the class effect of all therapeutic proteins, including mAbs.

Characterisation of the risk:

Frequency with 95% CI:

There were three events of immunogenicity in three patients treated with EPYSQLI (subject incidence: 6.383%; 95% CI: 1.336, 17.539) corresponding to an exposure-adjusted event rate of 12.796 events per 100 patient-years (95% CI: 2.639, 37.396). There were 13 events of immunogenicity in 11 patients treated with Soliris® (subject incidence: 23.404%; 95% CI: 12.303, 38.026), and the corresponding exposure-adjusted event rate was 66.252 events per 100 patient-years (95% CI: 35.276, 113.292).

Table SVII.3.1.1.10: Incidence and exposure-adjusted rate of immunogenicity TEAEs from the Phase III Study

Actual Treatment	Total subject, N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rate[b]	Exp-adj rate 95% CI
EPYSQLI	47	3 (6.383)	1.336, 17.539	23.444	3	12.796	2.639, 37.396
Soliris®	47	11 (23.404)	12.303, 38.026	19.622	13	66.252	35.276, 113.292

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Number and frequency of immunogenicity TEAEs from the Phase III Study

MedDRA PT	EPYSQLI N = 47	Soliris® N = 47
	n	n
Allergic transfusion reaction	0	1

MedDRA PT	EPYSQLI N = 47	Soliris® N = 47
	n	n
Dermatitis acneiform	0	1
Dermatitis allergic	1	1
Dermatitis atopic	0	1
Eczema	1	1
Erythema nodosum	0	1
Infusion site hypersensitivity	0	1
Mouth ulceration	0	1
Rash	0	2
Rash erythematous	0	1
Rhinitis allergic	0	1
Urticaria	1	1

N = Total subjects; n = No. of subjects with events

Seriousness/outcomes:

There were no serious events of immunogenicity in patients treated with EPYSQLI. There was one event of immunogenicity in one patient treated with Soliris® (subject incidence: 1.128%; 95% CI: 0.054, 11.294) corresponding to an exposure-adjusted event rate of 5.096 events per 100 patient-years (95% CI: 0.129, 28.395).

Table SVII.3.1.1.11: Incidence and exposure-adjusted rate of immunogenicity TEAEs that were serious from the Phase III Study

Actual Treatment	Total subject N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rate[b]	Exp-adj rate 95% CI
EPYSQLI	47	0	N/A	0	0	0	0
Soliris®	47	1 (2.128)	0.054, 11.294	19.622	1	5.096	0.129, 28.395

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Severity:

There were no severe events of immunogenicity in patients treated with EPYSQLI. In the Soliris® treatment group, one event of immunogenicity was reported to be severe in severity (5.096 events per 100 patient-years; 95% CI: 0.129, 28.395).

Table SVII.3.1.1.12: Incidence and exposure-adjusted rate of immunogenicity TEAEs that were severe from the Phase III Study

Actual Treatment	Total subject N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj Event rate[b]	Exp-adj rate 95% CI
EPYSQLI	47	0	N/A	0	0	0	0

Soliris®	47	1 (2.128)	0.054, 11.294	19.622	1	5.096	0.129, 28.395

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Reversibility and long-term outcomes:

Not yet established

Impact on quality of life:

None

Risk factors and risk groups:

No data were identified for risk factors for immunogenicity in patients with PNH or aHUS.

Preventability:

Not preventable

Refer to Part V.2 for a detailed description of additional risk minimisation measures for EPYSQLI, designed to minimise this risk.

Impact on the risk-benefit balance of the product:

Risk of immunogenicity is common to all biologicals. Patients may develop adenosine deaminase (ADA) which may or may not be clinically meaningful. Development of ADA may cause variable level of loss of drug's efficacy, but also results in serious adverse drug reaction (various allergic/hypersensitivity reactions in nature). No clinically meaningful outcomes resulting from the development of anti-eculizumab antibodies were described in the eculizumab clinical trials or in the post-marketing setting. The impact of this risk on EPYSQLI benefit-risk balance is acceptable in the light of anticipated benefits of the therapy.

Public health impact:

Immunogenicity to eculizumab could lead to the loss of activity and potentially severe immune reaction at the time of infusion.

Health care professionals are provided with educational material to inform them that administration of EPYSQLI may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis).

Limited impact on public health is expected for this important potential risk.

SVII.3.2 Presentation of the missing information

There is no missing information for eculizumab.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII. 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• *Meningococcal* infections • Serious infections (including sepsis) • *Aspergillus* infection • Infusion reactions • Severe TMA complications due to drug discontinuation in aHUS patients
Important potential risks	• Serious haemolysis after drug discontinuation in PNH patients • Immunogenicity
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for 'meningococcal infections'

This structured follow-up form is designed to optimise collection of all relevant information associated with the case reports of *meningococcal* infections to deepen the understanding of the factors leading to the risk associated with eculizumab.

This form collects detailed information about the patient, concerned medical product, patient's history with *meningococcal* infections and information about past vaccination/antibiotic prophylaxis. It further collects information on laboratory findings (bacteriology, serology, biopsy) and clinical presentation of the event. Finally, information about treatment and outcome of the event are collected.

The respective follow-up questionnaire form is provided in Annex 4 to the RMP.

Other forms of routine pharmacovigilance activities: None

III.2 Additional pharmacovigilance activities

There are no ongoing/planned additional pharmacovigilance activities.

In particular, as a proposed biosimilar, the MAH considers additional pharmacovigilance activities are not needed considering the established safety findings of Soliris® from the PNH and the aHUS registries .

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the MA				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional MA or a MA under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable as no post-authorisation efficacy studies are currently planned or imposed as specific obligations.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk	
Meningococcal infections	Routine risk communication: • SmPC sections 4.3, 4.4 and 4.8 • PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Vaccination/antibiotic prophylaxis is recommended in SmPC section 4.4 • Information on educational materials and signs and symptoms of meningococcal infections are included in SmPC section 4.4 • Signs and symptoms of meningococcal infections are closely described in PL section 2 Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription
Serious infections (including sepsis)	Routine risk communication: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Physicians should advise patients about gonorrhoea prevention Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription
Aspergillus infection	Routine risk communication: • SmPC sections 4.4 and 4.8 • PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk:

	No management measures are included in the SmPC and PL of eculizumab medicinal product for this safety concern Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription
Infusion reactions	Routine risk communication: • SmPC sections 4.2, 4.4 and 4.8 • PL sections 2, 3 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: No management measures are included in the SmPC and PL of eculizumab medicinal product for this safety concern Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription
Severe TMA complications due to drug discontinuation in aHUS patients	Routine risk communication: • SmPC section 4.4 • PL section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Monitoring of patients who discontinued EPYSQLI is recommended in SmPC section 4.4 and PL section 3 Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription
Important potential risk	
Serious haemolysis after drug discontinuation in PNH patients	Routine risk communication: • SmPC section 4.4 • PL section 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Monitoring of PNH patients who discontinue EPYSQLI is recommended and further specified in SmPC section 4.4 and PL section 3. Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription
Immunogenicity	Routine risk communication: • SmPC sections 4.4 and 4.8 • PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk:

	No management measures are included in the SmPC and PL of eculizumab medicinal product for this safety concern Other routine risk minimisation measures beyond the Product Information: Restricted medical prescription
Missing information	
None	

V.2. Additional Risk Minimisation Measures

a. Educational materials

Physician's Guide to Prescribing (PNH, aHUS)

Objectives:

To instruct HCPs about the detection, careful monitoring, and/or proper management of selected safety concerns associated with EPYSQLI.

To educate HCPs about *N. meningitidis* vaccines: to instruct HCP regarding re-vaccination according to manufacturers' direction through product information and national guidelines / recommendations.

To have all patients vaccinated at least two weeks prior to receiving EPYSQLI unless the risk of delaying EPYSQLI therapy outweighs the risks of developing a *meningococcal* infection and re-vaccinated periodically (according to manufacturers' product information and national guidelines / recommendations). Patients that cannot be vaccinated two weeks prior to receiving EPYSQLI must receive prophylactic antibiotics before and until two weeks after the vaccination.

- List of addressed safety concerns:

  Meningococcal infections

  Serious infections (including sepsis)

  Aspergillus infection

  Infusion reactions

  Serious haemolysis after drug discontinuation in PNH

  Immunogenicity

  Severe TMA complications due to drug discontinuation in aHUS patients

Rationale for the additional risk minimisation activity:

To inform HCPs regarding the main risks associated with eculizumab treatment, especially the risk of *meningococcal* infections that may lead to a fatal outcome. HCPs must educate their patients to seek immediate medical care as soon as they experience any signs and symptoms of *meningococcal* infections.

Target audience and planned distribution path:

Health care professionals using specific educational material that goes along with the controlled distribution of eculizumab.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable

PNH/aHUS Patient's Information Brochures

Objectives:

To educate patients about the detection and proper management of selected safety concerns associated with EPYSQLI.

To have all patients vaccinated at least 2 weeks prior to receiving EPYSQLI unless the risk of delaying EPYSQLI therapy outweighs the risks of developing a *meningococcal* infection and re-vaccinated periodically (according to manufacturers' product information and national guidelines / recommendations). Patients that cannot be vaccinated two weeks prior to receiving EPYSQLI must receive prophylactic antibiotics before and until two weeks after the vaccination.

To instruct patients and HCPs about the detection of possible *meningococcal* or general infection and steps to manage based on product information.

- List of addressed safety concerns:

  Meningococcal infections

  Serious infections (including sepsis)

  Infusion reactions

  Serious haemolysis after drug discontinuation in PNH

  Severe TMA complications due to drug discontinuation in aHUS patients

Rationale for the additional risk minimisation activity:

To inform patients about the main risks associated with eculizumab treatment, especially the risk of *meningococcal* infections that may lead to a fatal outcome. Patients must be trained to seek immediate medical care as soon as they experience any signs and symptoms of *meningococcal* infections and to carry and show their safety card at all time.

Target audience and planned distribution path:

PNH, aHUS patients

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable

PNH/aHUS Parent's Information Brochures

Objectives:

To educate paediatric patients' parents/legal guardians about the detection and proper management of selected safety concerns associated with EPYSQLI.

To have all patients vaccinated at least two weeks prior to receiving EPYSQLI unless the risk of delaying EPYSQLI therapy outweighs the risks of developing a *meningococcal* infection and re-vaccinated periodically (according to manufacturers' product information and national guidelines/ recommendations). Patients that cannot be vaccinated two weeks prior to receiving EPYSQLI must receive prophylactic antibiotics before and until two weeks after the vaccination.

To instruct patients' parents/legal guardians and HCPs about the detection of possible *meningococcal* or general infection and steps to manage based on product information.

- List of addressed safety concerns:

  Meningococcal infections

  Serious infections (including sepsis)

  Infusion reactions

  Serious haemolysis after drug discontinuation in PNH

  Severe TMA complications due to drug discontinuation in aHUS patients

Rationale for the additional risk minimisation activity:

To inform the legal guardians of paediatric patients about the main risks associated with eculizumab treatment, especially the risk of *meningococcal* infections that may lead to fatal outcome. Legal guardians of paediatric patients must be trained to seek immediate medical care as soon as they experience any signs and symptoms of *meningococcal* infections and to carry and show their safety card at all time.

Target audience and planned distribution path:

Legal guardians of paediatric patients with PNH, aHUS

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable

Patient Safety Card

Objectives:

To list signs and symptoms of *meningococcal* infections to help patients or their parents/legal guardians or other child carers to identify potential *meningococcal* infection and to seek immediately medical care. In addition, when patients present to a physician different than the usual prescriber, it helps to promptly identify potential *meningococcal* infection and to initiate appropriate antibiotic treatment.

- List of addressed safety concerns:

  Meningococcal infections

  Serious infections (including sepsis)

Rationale for the additional risk minimisation activity:

Signs and symptoms of *meningococcal* infections need to be recognised in a timely manner. This card highlights these signs and symptoms as well as the need for seeking immediate medical attention if they occur.

Target audience and planned distribution path:

Patients with PNH, aHUS

Physicians other than usual prescribers

Legal guardians and other child carers (e.g. school, day care services or persons, etc.)

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable

b. Controlled distribution

Objectives:

To ensure distribution of eculizumab only to eligible patients vaccinated against *N. meningitidis* or receiving appropriate prophylactic therapy.

- List of addressed safety concerns:

  Meningococcal infections

Rationale for the additional risk minimisation activity:

To highlight the importance of an effective vaccination against *meningococcal* infection to minimise this important risk.

Target audience and planned distribution path:

Prescribing physicians and pharmacists dispensing the drug

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable

c. Vaccination reminders for HCP

Objectives:

To remind prescribers to verify and ensure that their patients' vaccination against *meningococcal* infection are still current according to local vaccination guideline.

- List of addressed safety concerns:

  Meningococcal infection

Rationale for the additional risk minimisation activity:

To highlight the importance of an effective vaccination against *meningococcal* infection to minimise this important risk.

Target audience and planned distribution path:

Prescribing physicians

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Meningococcal infections	Routine risk minimisation measures: − SmPC sections 4.3, 4.4 and 4.8 − PL sections 2 and 4 Recommendations for vaccination/antibiotic prophylaxis in SmPC section 4.4 Signs and symptoms of meningococcal infections listed in SmPC section 4.4 and PL Section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational materials − Physician's guide − Patient's/Parent's information brochure − Patient safety card Controlled distribution Vaccination reminder	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Serious infections (including sepsis)	Routine risk minimisation measures: − SmPC sections 4.4 and 4.8 − PL sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Educational materials − Physician's guide − Patient's/Parent's information brochure − Patient safety card	
Aspergillus infection	Routine risk minimisation measures: − SmPC sections 4.4 and 4.8 − PL section 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational materials − Physician's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Infusion reactions	Routine risk minimisation measures: − SmPC sections 4.2, 4.4, and 4.8 − PL sections 2, 3, and 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational Materials − Physician's guide − Patient's/ Parent's information brochure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Severe TMA complications due to drug discontinuation in aHUS patients	Routine risk minimisation measures: − SmPC section 4.4 − PL section 3 Monitoring of patients who discontinued EPYSQLI recommended in SmPC section 4.4 and PL section 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational materials − Physician's guide (aHUS) − Patient's/Parent's information brochure (aHUS)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important potential risk		
Serious haemolysis after drug discontinuation in PNH patients	Routine risk minimisation measures: − SmPC section 4.4 − PL section 3 Monitoring of patients who discontinued EPYSQLI recommended in SmPC section 4.4 and PL section 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational materials − Physician's guide (PNH) − Patient's/Parent's information brochure (PNH)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Immunogenicity	Routine risk minimisation measures: − SmPC sections 4.4 and 4.8 − PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription. Additional risk minimisation measures: Educational materials − Physician's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information		
None		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Epysqli (eculizumab)

This is a summary of the risk management plan (RMP) for Epysqli. The RMP details important risks of Epysqli, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information) of Epysqli.

Summary of product characteristics (SmPC) of Epysqli and its package leaflet (PL) give essential information to Health Care Professionals and patients on how Epysqli should be used.

This summary of the RMP for Epysqli should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the RMP of Epysqli.

I. The medicine and what it is used for

Epysqli is indicated in adults and children for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS) (see SmPC for the full indication). It contains eculizumab as the active substance and it is given by Intravenous (IV) route of administration.

Further information about the evaluation of benefits can be found in EPAR of Epysqli, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Epysqli, together with measures to minimise such risks and the proposed studies for learning more about Epysqli risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Epysqli, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update reports assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Epysqli (eculizumab) are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Epysqli. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information	
Important identified risks	• Meningococcal infections • Serious infections (including sepsis) • Aspergillus infection • Infusion reactions • Severe TMA complications due to drug discontinuation in aHUS patients
Important potential risks	• Serious haemolysis after drug discontinuation in PNH patients • Immunogenicity
Missing information	None

II.B Summary of important risks

II.B.1 Important identified risk

Important Identified Risk: Meningococcal infections	
Evidence for linking the risk to the medicine	This identified risk is based on the results from the clinical development programme for eculizumab. Eculizumab mode of action is based on terminal complement Component 5 (C5) inhibition which is associated with an increased incidence of *meningococcal* infections caused by *Neisseria meningitidis*, as *meningococcus* is primarily cleared by the terminal complement components. Further evidence linking *meningococcal* infections to terminal complement inhibition can be found in the scientific literature.
Risk factors and risk groups	Main risk factors for these infections include: - Genetic deficiency or therapeutic inhibition of terminal complement - Lack of commercially available vaccine against certain *meningococcus* serogroup

	- (Partial) resistance of *meningococcal* strain to prophylactic antibiotics - Professionals who are exposed to environments of greater risk for *meningococcal* disease - Research, industrial, and clinical laboratory personnel who are routinely exposed to *N. meningitidis* - Military personnel during recruit training (military personnel may be at increased risk of *meningococcal* infection when accommodated in close quarters) - Day-care centre workers - Living on a college or university campus - Travelling to endemic areas for *meningococcal meningitis* (e.g. India, Sub-Saharan Africa, pilgrimage to Saudi Arabia for Hajj) No data were identified as additional risk factors for *meningococcal* infections related to underlying disease such as PNH or aHUS.
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC: Sections 4.3, 4.4 and 4.8 PL: Sections 2 and 4 Recommendations for vaccination/antibiotic prophylaxis in SmPC section 4.4 Signs and symptoms of meningococcal infections listed in SmPC section 4.4 and PL section 2 Restricted medical prescription <u>Additional risk minimisation measures:</u> Educational materials - Physician's guide (PNH, aHUS) - Patient's/Parent's information brochure (PNH, aHUS) - Patient safety card Controlled distribution Vaccination reminder
Additional pharmacovigilance activities	None
Important Identified Risk: Serious infections (including sepsis)	
Evidence for linking the risk to the medicine	This identified risk is based on the results from the clinical development programme for eculizumab. Eculizumab mode of action is based on terminal

	complement C5 inhibition, impacting in a minor way the ability to clear also infections other than *Neisseria spp*. infections in eculizumab-treated patients, potentially leading to serious infections and/or sepsis, even though this impact is significantly lower since early complement components are not affected by eculizumab. However, scientific literature shows that patients with terminal complement deficiency are only at increased risk of *Neisseria spp*. infections same as data from PNH registry of the originator (Soliris®) comparing treated and untreated patients which do not demonstrate association between eculizumab treatment and infections other than *Neisseria spp*. infections.
Risk factors and risk groups	Underlying immunodeficiency condition represents general risk factor for serious infection: either acquired (e.g. Aplastic Anaemia (AA) or Myelodysplastic syndrome (MDS) in patients with PNH or End-Stage Renal Disease in patients with aHUS) or due to other immunosuppressive drugs.
Risk minimisation measures	<u>Routine risk minimization measures:</u> SmPC: Sections 4.4 and 4.8 PL: Sections 2 and 4 Restricted medical prescription <u>Additional risk minimization measures:</u> Educational Material - Physician's guide (PNH, aHUS) - Patient's/Parent's information brochure (PNH, aHUS) - Patient safety card
Additional pharmacovigilance activities	None
Important Identified Risk: *Aspergillus* infection	
Evidence for linking the risk to the medicine	This identified risk is based on the results from the clinical development programme for eculizumab for prevention of antibody mediated rejection in kidney transplant recipients. Since host defence against *Aspergillus* infection is mainly driven by cellular immunity and complement component (C3a, C3b iC3b, and C5a), allowing chemotactism and opsonisation, eculizumab C5 blockade has only a partial effect on the host defence against *Aspergillus* infections and therefore, has been observed only in severely immunocompromised patients. Further evidence linking *aspergillosis* to immunocompromised states is provided in the scientific literature.

Risk factors and risk groups	Underlying severe immunodeficiency condition, acquired or due to other immunosuppressive drugs including steroids, exposure to construction or demolition, severe pancytopenia due AA, and pre-existing lung impairment or pre-existing *Aspergillus* infection.
Risk minimisation measures	Routine risk minimization measures: SmPC: Sections 4.4 and 4.8 PL: Section 4 Restricted medical prescription Additional risk minimization measures: Educational materials - Physician's guide (PNH, aHUS)
Additional pharmacovigilance activities	None
Important Identified Risk: Infusion reactions	
Evidence for linking the risk to the medicine	This identified risk is based on the observations made within the clinical development programme for eculizumab. As with all therapeutic proteins, administration of EPYSQLI may result in infusion reactions and could cause allergic or hypersensitivity reactions. Most of infusion-reactions which occurred in patients receiving eculizumab were non-serious and did not required discontinuation of eculizumab. In the post marketing setting anaphylactic / anaphylactoid reactions have been reported during or following eculizumab infusion. In PNH clinical studies, AEs were documented in the case report form as to whether they occurred within 24 or 48 hours of study medication.
Risk factors and risk groups	Patients with hypersensitivity to eculizumab, murine proteins or to any of the excipients. No data were identified for the risk factors for infusion reactions in patients with PNH or aHUS.
Risk minimisation measures	Routine risk minimization measures: SmPC: Sections 4.2, 4.4, and 4.8 PL: Sections 2, 3, and 4 Restricted medical prescription Additional risk minimization measures:

	Educational Materials - Physician's guide (PNH, aHUS) - Patient's/Parent's information brochure (PNH, aHUS)
Additional pharmacovigilance activities	None
Important Identified Risk: Severe TMA complications due to drug discontinuation in aHUS patients	
Evidence for linking the risk to the medicine	This risk resulted from the clinical development programme for eculizumab in aHUS patients. aHUS is a chronic and debilitating life-threatening disease due to life-long uncontrolled complement activation. Eculizumab treatment inhibits this otherwise uncontrolled complement activation. The discontinuation of eculizumab can result in signs and symptoms of severe TMA complications. The efficacy results from C11-003 observational study indicate that patients who discontinued eculizumab experience a higher rate of TMA complications (3-fold) compared to patients who never discontinued eculizumab treatment.
Risk factors and risk groups	Complement dysregulation due to genetic abnormalities or acquired deficiencies is associated with TMA.
Risk minimisation measures	Routine risk minimization measures: SmPC: Section 4.4 PL: Section 3 Restricted medical prescription Additional risk minimization measures: Educational Materials - Physician's guide (aHUS) Patient's/Parent's information brochure (aHUS)
Additional pharmacovigilance activities	None

II.B.2 Important potential risk

Important Potential Risk: Serious haemolysis after drug discontinuation in PNH patients	
Evidence for linking the risk to the medicine	This potential risk is a theoretical possibility in PNH patients, based on the mode of eculizumab action and nature of PNH.

Important Potential Risk: Serious haemolysis after drug discontinuation in PNH patients	
Risk factors and risk groups	No data were identified for risk factors for serious haemolysis due to drug discontinuation in patients with PNH.
Risk minimisation measures	Routine risk minimization measures: SmPC: Section 4.4 PL: Section 3 Monitoring of patients who discontinued EPYSQLI recommended in SmPC section 4.4 and PL section 3 Restricted medical prescription Additional risk minimization measures: Educational materials - Physician's guide (PNH) - Patient's/Parent's information brochure (PNH)
Additional pharmacovigilance activities	None
Important Potential Risk: Immunogenicity	
Evidence for linking the risk to the medicine	This potential risk is based on the known potential of all medicinal products and on the class effect of all therapeutic proteins, including mAbs.
Risk factors and risk groups	No data were identified for risk factors for immunogenicity in patients with PNH or aHUS.
Risk minimisation measures	Routine risk minimization measures: SmPC: Sections 4.4 and 4.8 PL: Section 2 Restricted medical prescription Additional risk minimization measures: Educational materials - Physician's guide (PNH, aHUS)
Additional pharmacovigilance activities	None

II.B.3 Missing information

None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Epysqli.

II.C.2 Other studies in post-authorisation development plan

None

PART VII: ANNEXES

PART VII: ANNEXES 61

Annex 1 – EudraVigilance Interface 62

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme 63

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan 64

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP 64

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP 64

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority 64

Annex 4 - Specific adverse drug reaction follow-up forms 65

Annex 5 - Protocols for proposed and on-going studies in RMP part IV 66

Annex 6 - Details of proposed additional risk minimisation activities 67

Annex 7 - Other supporting data (including referenced material) 69

Annex 8 – Summary of changes to the risk management plan over time 74

Annex 4 - Specific adverse drug reaction follow-up forms

Follow-up form for meningococcal infections

Questionnaire: Meningococcal Infection

The form is designed to provide information of patients who have suspected or confirmed meningococcal infection potentially associated with the Product
*Please enter all dates in the format MMM/DD/YYYY, e.g., JAN/01/2022

A. Safety Card

Patient presented their safety card to the health care provider at the time of treatment.

☐ Yes ☐ No ☐ Unknown

B. Patient Information

Date of Birth: M M M D D Y Y Y Y

Age (if known): _____

Or Age Category:

☐ Child (<12 years) ☐ Adolescent (12-17 years) ☐ Adults (18-65 years) ☐ Elderly (>65 years)

Gender:

☐ Male ☐ Female ☐ Unknown

Weight: ☐☐☐.☐ kg

Height: ☐☐☐.☐ cm

C. Product/Dosing Information

Product Name: _____ Product/Manufacturer/Lot no.: _____

Maintenance dosage: _____ Induction date and dosage: _____

Last dose date prior to the event: M M M D D Y Y Y Y

Action Taken with Product:

☐ No change ☐ Temporarily withdrawn ☐ Drug interrupted ☐ Withdrawn

☐ Dose increased ☐ Dose decreased ☐ Unknown ☐ Not Applicable

☐ Other (specify): _____

Questionnaire: Meningococcal Infection

D. Patient History

Previous history of meningococcal infection:

☐ Yes (*please describe*: _____) ☐ No ☐ Unknown

Risk factor for meningococcal infection:

☐ Yes (*please describe*: _____) ☐ No ☐ Unknown

(ex. Medical condition, exposure to laboratory, industry, close quarters, college campus, daycare workers, military, living in proximity or recent travel to endemic areas)

Meningococcal Vaccination: ☐ Yes *(If yes, provide vaccine name and date below)* ☐ No ☐ Unknown

Vaccine name: _____ ☐ Initial Vaccination Date: M M M D D Y Y Y Y

☐ Booster Vaccination Date: M M M D D Y Y Y Y

Vaccine name: _____ ☐ Initial Vaccination Date: M M M D D Y Y Y Y

☐ Booster Vaccination Date: M M M D D Y Y Y Y

Antibiotic prophylaxis: ☐ Yes *(If yes, provide information below)* ☐ No ☐ Unknown

If Yes, Antibiotic Name/Active substance:_____ Dosage / frequency: _____

Start date: M M M D D Y Y Y Y

Stop date: M M M D D Y Y Y Y ☐ Ongoing

Is the patient compliant with their antibiotic prophylaxis? ☐ Yes ☐ No ☐ Unknown

Questionnaire: Meningococcal Infection

E. Bacteriological Work Up

CSF (*Direct Exam Results*): _____

CSF (*Culture Results*): _____

CSF (*PCR Results*): _____

Blood (*Direct Exam Results*): _____

Blood (*Culture Results*): _____

Blood (*PCR Results*): _____

F. Clinical Presentation

Description of initial clinical signs and/or symptoms patient has presented with: _____

Onset Date of first symptom(s): | M | M | M | D | D | Y | Y | Y | Y |

Malaise	☐ Yes	☐ No	
Myalgia	☐ Yes	☐ No	
Fever	☐ Yes	☐ No	_____ *(If yes, please provide temp)*
Hypothermia	☐ Yes	☐ No	_____ *(If yes, please provide temp)*
Headache	☐ Yes	☐ No	
Neck stiffness	☐ Yes	☐ No	
Photophobia	☐ Yes	☐ No	
Vomiting	☐ Yes	☐ No	
Confusion	☐ Yes	☐ No	
Chills	☐ Yes	☐ No	
Convulsions	☐ Yes	☐ No	
Rash	☐ Yes	☐ No	_____ *(If yes, please specify type and localization)*
Other	☐ Yes	☐ No	_____ *(Please specify)*

Patients who receive(d) Antibiotic Prophylaxis Only

Minimum Inhibitory Concentration (MIC): _____

Questionnaire: Meningococcal Infection

G. Serology

Neisseria meningitidis serogroup/serotype: ☐ A ☐ B ☐ C ☐ W135 ☐ X ☐ Y ☐ Z

Other: _____

Neisseria meningitidis serosubtype (*If available*): _____

Neisseria meningitidis Genotyping (MLST, *if available*): _____

Meningococcal Antigen Typing System (MATS) assay (For serogroup B infection in patients vaccinated by 4CMenB):

_____

Skin biopsy culture:

☐ Done *(If done, results):* _____

☐ Not done

H. Treatment of the Event

Antibiotic name: _____ ☐ Ongoing Start date: M M M D D Y Y Y Y

M M M D D Y Y Y Y

Stop date:

Other medication:

Medication name: _____ ☐ Ongoing Start date: M M M D D Y Y Y Y

Stop date: M M M D D Y Y Y Y

Other supportive treatment:_____

Questionnaire: Meningococcal Infection

I. Outcome
☐ Unknown ☐ Recovered ☐ Recovered with sequelae *(specify)* _____ ☐ Ongoing ☐ Fatal *(specify cause of death)* _____
Additional Comments:

Annex 6 - Details of proposed additional risk minimisation activities

Approved key messages of the additional risk minimisation measures

Physician's educational material:

- Summary of products characteristics
- Physician's guide to prescribing

- **Physician's Guide to Prescribing:**
  - Treatment with eculizumab increases the risk of severe infection and sepsis, especially of *Neisseria meningitidis* and other *Neisseria* species, including disseminated gonorrhoea.
  - All patients must be monitored for signs of meningococcal infection.
  - The need for patients to be vaccinated against *Neisseria meningitidis* two weeks prior to receiving eculizumab and/or to receive antibiotic prophylaxis
  - The requirement to vaccinate children against pneumococcus and haemophilus before eculizumab treatments
  - There is an important risk of *Aspergillus* infection in patients treated with eculizumab. The HCPs should be advised to look for risk factors and signs and symptoms of *Aspergillus* infection. Practical advice should be included to mitigate the risk.
  - The risk of infusion reactions including anaphylaxis and advice on post-infusion monitoring
  - The risk of developing antibodies to eculizumab
  - Risk of serious haemolysis following eculizumab discontinuation and postponement of administration, its criteria, the required post-treatment monitoring and its proposed management (PNH only).
  - Risk of severe thrombotic microangiopathic complications following eculizumab discontinuation and postponement of administration, its signs, symptoms, monitoring and management (aHUS only)
  - The need to explain to and ensure understanding of by patients
    - the risks of treatment with eculizumab
    - the signs and symptoms of sepsis/severe infection and what action to take
    - the patient's/parent's guides and their contents
    - the need to carry the patient safety card and to tell any healthcare practitioner that he/she is receiving treatment with eculizumab
    - the requirement for pre-treatment vaccinations/antibiotic prophylaxis

Patient's/Parent's educational material:

- Package leaflet
- Patient's/parent's information brochures
- Patient safety card

- **Patient's/Parent's Information Brochure**
  - Treatment with eculizumab increases the risk of severe infection, especially Neisseria meningitidis and other Neisseria species, including disseminated gonorrhoea
  - Signs and symptoms of severe infection and the need to obtain urgent medical care
  - The patient safety card and the need to carry it on their person and tell any treating HCP that they are being treated with eculizumab
  - The importance of meningococcal vaccination prior to treatment and/or to receive antibiotic prophylaxis
  - The need for children to be vaccinated against pneumococcus and haemophilus before eculizumab treatment
  - The risk of infusion reactions with eculizumab, including anaphylaxis, and the need for clinical monitoring post-infusion
  - Risk of severe TMA complications (in aHUS) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations
  - Risk of severe haemolysis (in PNH) following discontinuation/postponement of eculizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing eculizumab administrations

- **Patient Safety Card**
  - Signs and symptoms of infection and sepsis
  - Warning to seek immediate medical care if above are present
  - Statement that the patient is receiving eculizumab
  - Contact details where a health care practitioner can receive further information