EUROPEAN UNION RISK MANAGEMENT PLAN

BEKEMV™ (ABP 959, eculizumab)

Marketing Authorization Holder:	Amgen Technology (Ireland) Unlimited Company Pottery Road, Dun Laoghaire Co. Dublin A96 F2A8 Ireland
Version:	2.0
Date:	13 August 2025
Supersedes:	Version 1.1, dated 15 April 2024

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	2.0
Data lock point of this RMP:	01 October 2024
Date of final sign-off:	13 August 2025
Rationale for submitting an updated RMP:	To align with the reference product Soliris® by: • Removing the Important identified risk of 'Aspergillus infection' • Removing the Important potential risks of 'Serious hemolysis after drug discontinuation in paroxysmal nocturnal hemoglobinuria patients' and 'Immunogenicity' • Revising the risk minimization measures

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
PART II: Safety Specifications		
SV: Postauthorization Experience	Added the postmarketing exposure data from launch to a data cut-off of 01 October 2024	Version 2.0, 13 August 2025
SVII: Identified and Potential Risks	Removed the following important risks from the list of safety concerns: • Important identified risk: o *Aspergillus* Infection • Important potential risks: o Serious hemolysis after drug discontinuation in paroxysmal nocturnal hemoglobinuria patients o Immunogenicity	Version 2.0, 13 August 2025
SVIII: Summary of the Safety Concerns	Updated to align with the changes in Module SVII	Version 2.0, 13 August 2025
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	• Updated to align with the changes in Module SVII • Revised the additional risk minimization measures	Version 2.0, 13 August 2025
Part VI: Summary of the Risk Management Plan	Updated to align with the changes in Module SVII	Version 2.0, 13 August 2025
Part VII: Annexes		
Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)	Updated the key messages of the revised additional risk minimization measures	Version 2.0, 13 August 2025
Annex 8: Summary of Changes to the Risk Management Plan Over Time	Updated to align with the changes described above	Version 2.0, 13 August 2025

Other RMP versions under evaluation:	
RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	1.1
Approved with procedure:	EMEA/H/C/005652/IB/0004
Date of approval (opinion date):	07 May 2024
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
aHUS	atypical hemolytic uremic syndrome
ATC	Anatomical Therapeutic Chemical
BLA	Biologics License Application
C5	complement protein 5
CHO	Chinese hamster ovary
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
HFI	hereditary fructose intolerance
INN	International Nonproprietary Name
MAH	marketing authorization holder
PL	package leaflet
PNH	paroxysmal nocturnal hemoglobinuria
PSUR	Periodic Safety Update Report
RMP	risk management plan
SmPC	Summary of Product Characteristics
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
TMA	thrombotic microangiopathy complications
US	United States

Note to Reviewers: ABP 959 has been developed as a biosimilar candidate to Soliris® (eculizumab). Soliris (eculizumab) that is approved in, and sourced from, the United States (US) is referred to as “eculizumab (US).” Soliris (eculizumab) that is approved in, and sourced from, the European Union (EU) is referred to as “eculizumab (EU).” The comparator reference medicinal product Soliris is referred to as eculizumab in the ABP 959 studies to be consistent with the marketing application. In all other contexts in this document it is referred to as Soliris. The biosimilar candidate to Soliris is referred to as ABP 959 in the Amgen-sponsored studies to be consistent with the marketing application. In all other contexts in this document it is referred to as BEKEMV.

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Eculizumab
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Selective immunosuppressants, ATC code: L04AJ01
Marketing authorization holder	Amgen Technology (Ireland) UC
Medicinal products to which this risk management plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	BEKEMV
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	BEKEMV is a humanized monoclonal ($IgG_{2/4κ}$) antibody.
Summary of mode of action	Eculizumab, the active substance in BEKEMV, 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 opsonization of microorganisms and clearance of immune complexes.
Important information about its composition	BEKEMV is produced in Chinese hamster ovary (CHO) cell line by recombinant DNA technology.
Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.
Indication(s) in the EEA	
Current	BEKEMV is indicated in adults and children for the treatment of: • Paroxysmal nocturnal hemoglobinuria (PNH). Evidence of clinical benefit is demonstrated in patients with hemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history. • Atypical hemolytic uremic syndrome (aHUS).
Proposed (if applicable)	Not applicable

Table 1. Product(s) Overview

<table>
<tr><td>Dosage in the EEA

Current</td><td>
<u>PNH in adults</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 BEKEMV administered via a 25 to 45 minute (35 minutes ± 10 minutes) intravenous infusion every week for the first 4 weeks.
• Maintenance phase: 900 mg of BEKEMV administered via a 25 to 45 minute (35 minutes ± 10 minutes) intravenous infusion for the fifth week, followed by 900 mg of BEKEMV administered via a 25 to 45 minute (35 minutes ± 10 minutes) intravenous infusion every 14 ± 2 days.
<u>aHUS in adults</u>
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 BEKEMV administered via a 25 to 45 minute (35 minutes ± 10 minutes) intravenous infusion every week for the first 4 weeks.
• Maintenance phase: 1200 mg of BEKEMV administered via a 25 to 45 minute (35 minutes ± 10 minutes) intravenous infusion for the fifth week, followed by 1200 mg of BEKEMV administered via a 25 to 45 minute (35 minutes ± 10 minutes) intravenous infusion every 14 ± 2 days.
<u>Pediatric Patients in PNH and aHUS</u>
BEKEMV is contraindicated in children below 2 years of age.
Pediatric PNH and aHUS patients with body weight ≥ 40 kg are treated with the adult dosing recommendations, respectively.
In pediatric PNH and aHUS patients above 2 years of age and with body weight below 40 kg, the BEKEMV 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 for the first 2 weeks</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 for the first 2 weeks</td><td>600 mg at week 3; then 600 mg every 2 weeks</td></tr>
<tr><td>10 to < 20 kg</td><td>600 mg single dose at week 1</td><td>300 mg at week 2; then 300 mg every 2 weeks</td></tr>
<tr><td>5 to < 10 kg</td><td>300 mg single dose at week 1</td><td>300 mg at week 2; then 300 mg every 3 weeks</td></tr>
</table>
Subjects who undergo plasma exchange may receive additional doses of BEKEMV
</td></tr>
</table>

Table 1. Product(s) Overview

Dosage in the EEA (continued)	
Proposed (if applicable)	Not applicable
Pharmaceutical form(s) and strength(s)	
Current	BEKEMV is supplied as a clear to opalescent, colorless to slightly yellow, pH 5.2, concentrate for solution for infusion in a vial of 30 mL containing 300 mg of eculizumab (10 mg/mL). After dilution, the final concentration of the solution to be infused is 5 mg/mL.
Proposed (if applicable)	Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

As per the Guideline on Good Pharmacovigilance Practices Module V - Risk management systems (EMA/838713/2011 Rev 2), Module SI may be omitted from the EU Risk Management Plan (RMP) for new applications for similar biological products.

Part II: Module SII - Nonclinical Part of the Safety Specification

ABP 959 has been developed as a biosimilar candidate to Soliris (eculizumab), the reference medicinal product. Analytical studies and in vitro pharmacology studies have been conducted to support biosimilarity. Comparability of ABP 959 to Soliris, the reference medicinal product, has been established through physicochemical and biological characterization studies, as recommended in the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1). No animal toxicology studies with ABP 959 were conducted since there was no residual uncertainty regarding the safety of ABP 959 in patients.

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from ABP 959 studies		
Toxicity		
Key issues identified from acute or repeat-dose toxicity studies	ABP 959 was not evaluated in single- or repeat-dose in vivo toxicology studies given the lack of a pharmacologically relevant species and given no residual uncertainty in comparative analytical similarity assessment (inclusive of comprehensive in vitro functional evaluation) and supplementary comparative ex vivo pharmacology studies. Exclusion of toxicology studies when no uncertainties remain about the safety of ABP 959 is also in alignment with regulatory guidance for biosimilar development (European Medicines Agency [EMA] Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues, EMA/CHMP/BMWP/403543, 2012).	ABP 959 is a medicinal product which is biosimilar to Soliris. Soliris has been in clinical use as a marketed medicinal product for over 10 years.
Reproductive/ developmental toxicity	Reproductive and developmental toxicity studies were not conducted with ABP 959 in alignment with regulatory guidance for biosimilar development and given no residual uncertainty in comparative analytical similarity assessment (inclusive of comprehensive in vitro functional evaluation), supplementary comparative ex vivo pharmacology studies, or safety (EMA/CHMP/BMWP/403543, 2012).	As a biosimilar medicinal product, the observed effects of Soliris are expected for ABP 959.

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from ABP 959 studies (continued)		
Toxicity		
Genotoxicity	No studies evaluating the genotoxic or mutagenic potential of ABP 959 have been conducted. According to the current guidelines on the preclinical safety evaluation of biotechnology-derived pharmaceuticals (International Conference on Harmonisation [ICH] S6[R1], Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals, 2011) and consistent with guidelines for biosimilar products, the range and type of standard genotoxicity studies routinely conducted for pharmaceuticals are not applicable for biotechnology-derived pharmaceuticals.	Not applicable.
Carcinogenicity	No studies evaluating the carcinogenic potential of ABP 959 have been conducted in alignment with regulatory guidance for biosimilar and biotechnology-derived pharmaceutical development (EMA/CHMP/BMWP/403543, 2012; ICH S6[R1], Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals, 2011) and given no residual uncertainty in comparative analytical similarity assessment (inclusive of comprehensive in vitro functional evaluation), supplementary comparative ex vivo pharmacology studies, or safety.	Not applicable.

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Nonclinical safety findings from Soliris studies		
Toxicity		
Key issues identified from acute or repeat-dose toxicity studies	Eculizumab is a highly specific monoclonal antibody (mAb) binding only to human C5 and not to C5 from any other mammalian species tested. In a 26-week toxicity study performed in mice using a murine anti-C5 surrogate mAb BB5.1, treatment did not affect any of the toxicity parameters examined (Soliris Summary of Product Characteristics [SmPC]; EMA European Public Assessment Report [EPAR] Scientific Discussion, 2007).	Not applicable.
Reproductive/ developmental toxicity	Animal reproduction studies have not been conducted with eculizumab due to lack of pharmacologic activity in non-human species. No clear treatment-related effects or adverse effects were observed in reproductive toxicology studies in mice with the murine anti-C5 surrogate mAb BB5.1, which was utilized to assess the reproductive safety of C5 blockade. These studies included assessment of fertility and early embryonic development, developmental toxicity, and pre- and postnatal development (Soliris SmPC; EMA EPAR Scientific Discussion, 2007). When maternal exposure to the antibody occurred during organogenesis, 2 cases of retinal dysplasia and 1 case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose (approximately 4 times the maximum recommended human Soliris dose, based on a body weight comparison); however, the exposure did not increase fetal loss or neonatal death (Soliris SmPC). Intravenous injections of murine antiC5 surrogate mAb BB5.1 administered to male and female mice had no effects on mating or fertility (Food and Drug Administration [FDA] Biologics License Application [BLA] 125166, 2007; EMA EPAR Scientific Discussion, 2007).	No effects on the breastfed newborn/infant are anticipated as limited data available suggest that eculizumab is not excreted in human breast milk. However, due to the limitations of the available data, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for eculizumab and any potential adverse effects on the breastfed child from eculizumab or from the underlying maternal condition. Therefore, Soliris should be given to a pregnant woman only if clearly needed. Women of childbearing potential are advised to use adequate contraception to prevent pregnancy during and for at least 5 months after the last dose of treatment with eculizumab (Soliris SmPC).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Nonclinical safety findings from Soliris studies (continued)		
Toxicity		
Genotoxicity and carcinogenicity	No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of eculizumab (Soliris SmPC; EMA EPAR Scientific Discussion, 2007). The 26-week repeat-dose toxicity study in mice with the murine anti-C5 surrogate mAb BB5.1 showed no cytotoxic or proliferative activities suggestive of carcinogenic risk at dose levels up to 60 mg/kg/week (ie, a dose level showing significant inhibition of C5 activation) (EMA EPAR Scientific Discussion, 2007).	Not applicable.
Other toxicity-related information or data		
Immunotoxicity	There were no remarkable macroscopic observations or histomorphological findings in mandibular or mesenteric lymph nodes related to treatment with the murine surrogate anti-C5 mAb BB5.1, in the 26-week mouse study (EMA EPAR Scientific Discussion, 2007).	Not applicable.

Part II: Module SIII - Clinical Trial Exposure

Table 3. Total Subject Exposure to ABP 959 or Eculizumab in Clinical Trials by Indication and Duration (Safety Analysis Set)

	ABP 959		Eculizumab	
Indication	Cumulative Exposure < 6 months n (subj-yrs)	Cumulative Exposure ≥ 6 months n (subj-yrs)	Cumulative Exposure < 6 months n (subj-yrs)	Cumulative Exposure ≥ 6 months n (subj-yrs)
Phase 1 PK/PD study in healthy volunteers	71 (2.92)	0 (0)	146 (6.00)	0 (0)
Phase 3 Paroxysmal Nocturnal Hemoglobinuria (PNH)	5 (2.06)	36 (28.05)	6 (2.35)	36 (28.48)
Total	76 (4.98)	36 (28.05)	152 (8.34)	36 (28.48)

n = number of subjects exposed to ABP 959 or eculizumab; PD = pharmacodynamic; PK = pharmacokinetic; subj-yrs = total subject-years of follow-up
Note: Data is from the completed phase 1 PK/PD Study 20150164 (completed on 26Mar2017 with the planned study duration of 57 days) and the completed phase 3 PNH Study 20150168 (completed on 12July2022 with the planned study duration of 553 days).
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
For Phase 1 study, duration of exposure is calculated as (minimum of (the last dose date + 14, end of study date) - first dose date +1)/365.25.
For Phase 3 study, for subjects who received treatment after crossover, duration of exposure before crossover is calculated as (first dose date after crossover - first dose date)/365.25; for subjects who did not crossover or received treatment after crossover, duration of exposure before crossover is calculated as (minimum of (lastdose date + 14, end of study date) - first dose date +1)/365.25.
Their exposures are summarized under the treatment column defined by the actual treatment received before crossover.
Duration of exposure after crossover is calculated as (minimum of (last dose date + 14, end of study date) - first dose date after crossover +1)/365.25 and is summarized under the treatment column defined by the actual treatment received after crossover.
Source Dataset: ADSL, Program: t-cum-subj-exp.sas, Output: t03-cum-subj-exp.rtf, Generated on: 17OCT2022 09:59

Table 4. Total Subject Exposure to ABP 959 or Eculizumab in Clinical Trials by Indication, Age Group, and Gender (Safety Analysis Set)

	ABP 959		Eculizumab	
Indication	< 65 years n (subj-yrs)	≥ 65 years n (subj-yrs)	< 65 years n (subj-yrs)	≥ 65 years n (subj-yrs)
Male				
Phase 1 PK/PD study in healthy volunteers	71 (2.92)	0 (0)	146 (6.00)	0 (0)
Phase 3 Paroxysmal Nocturnal Hemoglobinuria (PNH) study	17 (11.11)	3 (2.98)	17 (13.97)	3 (1.13)
Total	88 (14.02)	3 (2.98)	163 (19.97)	3 (1.13)
Female				
Phase 1 PK/PD study in healthy volunteers	0 (0)	0 (0)	0 (0)	0 (0)
Phase 3 Paroxysmal Nocturnal Hemoglobinuria (PNH) study	13 (11.03)	8 (4.99)	13 (8.49)	9 (7.23)
Total	13 (11.03)	8 (4.99)	13 (8.49)	9 (7.23)

n = number of subjects exposed to ABP 959 or eculizumab; PD = pharmacodynamic; PK = pharmacokinetic; subj-yrs = total subject-years of follow-up

Note: Data is from the completed phase 1 PK/PD Study 20150164 (completed on 26Mar2017 with the planned study duration of 57 days) and the completed phase 3 PNH Study 20150168 (completed on 12July2022 with the planned study duration of 553 days).

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

For Phase 1 study, duration of exposure is calculated as (minimum of (the last dose date + 14, end of study date) - first dose date +1)/365.25.

For Phase 3 study, for subjects who received treatment after crossover, duration of exposure before crossover is calculated as (first dose date after crossover - first dose date)/365.25; for subjects who did not crossover or received treatment after crossover, duration of exposure before crossover is calculated as (minimum of (lastdose date + 14, end of study date) - first dose date+1)/365.25.

Their exposures are summarized under the treatment column defined by the actual treatment received before crossover.

Duration of exposure after crossover is calculated as (minimum of (last dose date + 14, end of study date) - first dose date after crossover +1)/365.25 and is summarized under the treatment column defined by the actual treatment received after crossover.

Source Dataset: ADSL, Program: t-cum-subj-exp-age-sex.sas, Output: t04-cum-subj-exp-age-sex.rtf, Generated on: 17OCT2022 10:29

Table 5. Exposure to ABP 959 or Eculizumab in Clinical Trials by Dose Level and Indication (Safety Analysis Set)

	Exposure to ABP 959 in Days			Exposure to Eculizumab in Days			Exposure to ABP 959 in Subject-years			Exposure to Eculizumab in Subject-years		
Indication	300 mg Single Dose n (mean)	900 mg Q2W n (mean)	1200 mg Q2W n (mean)	300 mg Single Dose n (mean)	900 mg Q2W n (mean)	1200 mg Q2W n (mean)	300 mg Single Dose n (total)	900 mg Q2W n (total)	1200 mg Q2W n (total)	300 mg Single Dose n (total)	900 mg Q2W n (total)	1200 mg Q2W n (total)
Phase 1 PK/PD study in healthy volunteers	71 (15.0)	0 (0)	0 (0)	146 (15.0)	0 (0)	0 (0)	71 (2.92)	0 (0)	0 (0)	146 (6.00)	0 (0)	0 (0)
Phase 3 Paroxysmal Nocturnal Hemoglobinuria (PNH)	0 (0)	41 (267.0)	1 (54.0)	0 (0)	42 (268.0)	0 (0)	0 (0)	41 (29.97)	1 (0.15)	0 (0)	42 (30.82)	0 (0)
Total	71 (15.0)	41 (267.0)	1 (54.0)	146 (15.0)	42 (268.0)	0 (0)	71 (2.92)	41 (29.97)	1 (0.15)	146 (6.00)	42 (30.82)	0 (0)

n = number of subjects exposed to ABP 959 or eculizumab; PD = pharmacodynamic; PK = pharmacokinetic; subj-yrs = total subject-years of follow-up

Note: Data is from the completed phase 1 PK/PD Study 20150164 (completed on 26Mar2017 with the planned study duration of 57 days) and the completed phase 3 PNH Study 20150168 (completed on 12July2022 with the planned study duration of 553 days).

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

For Phase 1 study, duration of exposure is calculated as (minimum of (the last dose date + 14, end of study date) - first dose date +1)/365.25.

For Phase 3 study, for subjects who received treatment after crossover, duration of exposure before crossover is calculated as (first dose date after crossover - first dose date)/365.25; for subjects who did not crossover or received treatment after crossover, duration of exposure before crossover is calculated as (minimum of (lastdose date + 14, end of study date) - first dose date+1)/365.25. Their exposures are summarized under the treatment column defined by the actual treatment received before crossover. Duration of exposure after crossover is calculated as (minimum of (last dose date + 14, end of study date) - first dose date after crossover +1)/365.25 and is summarized under the treatment column defined by the actual treatment received after crossover.

For subjects who required a temporary dose adjustment of investigational product (from 900 mg Q2W to 1200 mg Q2W) based on signs and symptoms of intravascular hemolysis, their duration of exposure while receiving 1200 Q2W dose is defined as the sum of time from the date of the first 1200 Q2W dose to earlier of the day before resuming 900 Q2W dose or 14 days after the last 1200 Q2W dose for each incident of dose adjustment, and is summarized under the 1200 mg Q2W column. Their duration of exposure while receiving 900 mg Q2W is defined as the duration of exposure during the study minus the duration of exposure while receiving 1200 Q2W dose, and is summarized under the 900 mg Q2W column. These subjects are counted in the “n” for both columns.

Source Dataset: ADSL, Program: t--exp-by-dose.sas, Output: .rtf, Generated on: 17OCT2022 10:14

Table 6. Total Subject Exposure to ABP 959 or Eculizumab in Clinical Trials by Product and Race/Ethnic Group (Safety Analysis Set)

Indication	ABP 959 n (subj-yrs)	Eculizumab n (subj-yrs)
Phase 1 PK/PD study in healthy volunteers		
Ethnic		
Hispanic or Latino	9 (0.37)	16 (0.66)
Not Hispanic or Latino	62 (2.55)	130 (5.34)
Total	71 (2.92)	146 (6.00)
Race		
Asian	15 (0.62)	42 (1.72)
Black or African American	1 (0.04)	6 (0.25)
White	51 (2.09)	92 (3.78)
Other	4 (0.16)	6 (0.25)
Total	71 (2.92)	146 (6.00)

n = number of subjects exposed to ABP 959 or eculizumab; PD = pharmacodynamic; PK = pharmacokinetic; subj-yrs = total subject-years of follow-up
Note: Data is from the completed phase 1 PK/PD Study 20150164 (completed on 26Mar2017 with the planned study duration of 57 days) and the completed phase 3 PNH Study 20150168 (completed on 12July2022 with the planned study duration of 553 days).
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
For Phase 1 study, duration of exposure is calculated as (minimum of (the last dose date + 14, end of study date) - first dose date +1)/365.25.
For Phase 3 study, for subjects who received treatment after crossover, duration of exposure before crossover is calculated as (first dose date after crossover - first dose date)/365.25; for subjects who did not crossover or received treatment after crossover, duration of exposure before crossover is calculated as (minimum of (lastdose date + 14, end of study date) - first dose date+1)/365.25.
Their exposures are summarized under the treatment column defined by the actual treatment received before crossover.
Duration of exposure after crossover is calculated as (minimum of (last dose date + 14, end of study date) - first dose date after crossover +1)/365.25 and is summarized under the treatment column defined by the actual treatment received after crossover.
Source Dataset: ADSL, Program: t-cum-subj-exp-ethnic-race.sas, Output: t06-cum-subj-exp-ethnic-race.rtf, Generated on: 17OCT2022 10:03

Table 6. Total Subject Exposure to ABP 959 or Eculizumab in Clinical Trials by Product and Race/Ethnic Group (Safety Analysis Set)

Indication	ABP 959 n (subj-yrs)	Eculizumab n (subj-yrs)
Phase 3 Paroxysmal Nocturnal Hemoglobinuria (PNH) study		
Ethnic		
Hispanic or Latino	1 (0.08)	1 (1.00)
Not Hispanic or Latino	27 (20.52)	27 (19.59)
Not Reported	5 (3.02)	5 (4.49)
Not allowed to collect	7 (5.49)	8 (5.24)
Unknown	1 (1.00)	1 (0.50)
Total	41 (30.11)	42 (30.82)
Race		
Asian	1 (0.52)	1 (1.00)
White	33 (24.10)	33 (24.59)
Not allowed to collect	7 (5.49)	8 (5.24)
Total	41 (30.11)	42 (30.82)

n = number of subjects exposed to ABP 959 or eculizumab; PD = pharmacodynamic; PK = pharmacokinetic; subj-yrs = total subject-years of follow-up
Note: Data is from the completed phase 1 PK/PD Study 20150164 (completed on 26Mar2017 with the planned study duration of 57 days) and the completed phase 3 PNH Study 20150168 (completed on 12July2022 with the planned study duration of 553 days).
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
For Phase 1 study, duration of exposure is calculated as (minimum of (the last dose date + 14, end of study date) - first dose date +1)/365.25.
For Phase 3 study, for subjects who received treatment after crossover, duration of exposure before crossover is calculated as (first dose date after crossover - first dose date)/365.25; for subjects who did not crossover or received treatment after crossover, duration of exposure before crossover is calculated as (minimum of (lastdose date + 14, end of study date) - first dose date+1)/365.25.
Their exposures are summarized under the treatment column defined by the actual treatment received before crossover.
Duration of exposure after crossover is calculated as (minimum of (last dose date + 14, end of study date) - first dose date after crossover +1)/365.25 and is summarized under the treatment column defined by the actual treatment received after crossover.
Source Dataset: ADSL, Program: t-cum-subj-exp-ethnic-race.sas, Output: t06-cum-subj-exp-ethnic-race.rtf, Generated on: 17OCT2022 10:03

Table 6. Total Subject Exposure to ABP 959 or Eculizumab in Clinical Trials by Product and Race/Ethnic Group (Safety Analysis Set)

Indication	ABP 959 n (subj-yrs)	Eculizumab n (subj-yrs)
Total		
Ethnic		
Hispanic or Latino	10 (0.45)	17 (1.65)
Not Hispanic or Latino	89 (23.07)	157 (24.93)
Not Reported	5 (3.02)	5 (4.49)
Not allowed to collect	7 (5.49)	8 (5.24)
Unknown	1 (1.00)	1 (0.50)
Total	112 (33.03)	188 (36.82)
Race		
Asian	16 (1.14)	43 (2.72)
Black or African American	1 (0.04)	6 (0.25)
White	84 (26.20)	125 (28.36)
Other	4 (0.16)	6 (0.25)
Not allowed to collect	7 (5.49)	8 (5.24)
Total	112 (33.03)	188 (36.82)

n = number of subjects exposed to ABP 959 or eculizumab; PD = pharmacodynamic; PK = pharmacokinetic; subj-yrs = total subject-years of follow-up
Note: Data is from the completed phase 1 PK/PD Study 20150164 (completed on 26Mar2017 with the planned study duration of 57 days) and the completed phase 3 PNH Study 20150168 (completed on 12July2022 with the planned study duration of 553 days).
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
For Phase 1 study, duration of exposure is calculated as (minimum of (the last dose date + 14, end of study date) - first dose date +1)/365.25.
For Phase 3 study, for subjects who received treatment after crossover, duration of exposure before crossover is calculated as (first dose date after crossover - first dose date)/365.25; for subjects who did not crossover or received treatment after crossover, duration of exposure before crossover is calculated as (minimum of (lastdose date + 14, end of study date) - first dose date+1)/365.25.
Their exposures are summarized under the treatment column defined by the actual treatment received before crossover.
Duration of exposure after crossover is calculated as (minimum of (last dose date + 14, end of study date) - first dose date after crossover +1)/365.25 and is summarized under the treatment column defined by the actual treatment received after crossover.
Source Dataset: ADSL, Program: t-cum-subj-exp-ethnic-race.sas, Output: t06-cum-subj-exp-ethnic-race.rtf, Generated on: 17OCT2022 10:03

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

ABP 959 has been developed as a biosimilar for Soliris. Table 7 reflects the important exclusion criteria for ABP 959.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Hypersensitivity to any constituent of the product, including mammalian cell-derived drug products	This is a contraindication for ABP 959 and the reference medicinal product, Soliris.	No	It is contraindicated in patients with known hypersensitivity to eculizumab or to any of the excipients. It is contraindicated for the reference medicinal product, Soliris.
History of meningococcal infection	This is a contraindication for ABP 959 and the reference medicinal product, Soliris.	No	The patients' susceptibility to meningococcal infection is increased. In line with the reference medicinal product, Soliris, treatment is contraindicated in patients with unresolved *Neisseria meningitidis* infection or who are not currently vaccinated against *Neisseria meningitidis* (unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination).
Presence or suspicion of active bacterial infection, or recurrent bacterial infection	Due to the mechanism of action, there is an increased risk for bacterial infections with ABP 959 and the reference medicinal product, Soliris.	No	Patients may have increased susceptibility to infections, especially with *Neisseria spp.* (other than *Neisseria meningitidis*) and encapsulated bacteria. In line with the reference medicinal product, Soliris, cautionary language concerning use in patients with active systemic infections is addressed in SmPC Section 4.4, Special warnings and precautions for use.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Human immunodeficiency virus positive	Due to the mechanism of action, there is an increased risk for bacterial infections with ABP 959 and the reference medicinal product, Soliris.	No	Human immunodeficiency virus may increase the patient's risk of infections. In line with the reference medicinal product, Soliris, cautionary language concerning use in patients with active systemic infections is addressed in SmPC Section 4.4, Special warnings and precautions for use.
Pregnancy and breastfeeding	Human immunoglobulin G is known to cross the human placental barrier, and thus ABP 959 may potentially cause terminal complement inhibition in the fetal circulation.	No	There are no well-controlled studies in pregnant women. Effective contraception should be used in women who are of childbearing potential, for up to 5 months after use. In line with the reference medicinal product, Soliris, treatment should be given to a pregnant woman only if the benefit outweighs the risks. No effects on the breastfed newborn/infant are anticipated as limited data available suggest that eculizumab is not excreted in human breast milk. However, due to the limitations of the available data, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for eculizumab and any potential adverse effects on the breastfed child from eculizumab or from the underlying maternal condition. In line with the reference medicinal product, Soliris, treatment should be given to a breastfeeding woman only if the benefit outweighs the risks.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Male subjects with female partners of childbearing potential unwilling to follow indicated contraceptive measures	To ensure that the evaluation of the safety in clinical studies was not affected	No	No studies have been performed to determine the effects of eculizumab in the sperm. This restriction is not necessary if male patients and their female sexual partners of childbearing potential use indicated contraceptive measures.
Hereditary complement deficiency	As a primary immunodeficiency, subjects with known or suspected hereditary complement deficiency have increased risk of severe infections, including *Neisseria meningitidis*.	No	Due to the mechanism of action, the patients' susceptibility to meningococcal infection is increased. In line with the reference medicinal product, Soliris, treatment is contraindicated in patients with unresolved *Neisseria meningitidis* infection or who are not currently vaccinated against *Neisseria meningitidis* (unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination).
Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure [New York Heart Association ≥ Class III], serious uncontrolled cardiac arrhythmia), peripheral vascular disease, cerebrovascular accident, or transient ischemic attack in the previous 6 months	To ensure that the evaluation of the safety and efficacy profile in clinical studies was not affected, since subjects with clinically significant cardiovascular disease require intensive treatment for the underlying disease, which can preclude them from keeping to the schedule of planned visits, treatments, and evaluations.	No	Patients with underlying disease may still derive benefit from treatment with BEKEMV and the use of BEKEMV in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Evidence of acute thrombosis (liver Doppler ultrasound of hepatic and portal veins)	To ensure that the evaluation of the safety and efficacy profile in clinical studies was not affected. The target population with PNH has an increased risk for thrombosis, particularly in hepatic and portal veins.	No	Recent thrombosis in hepatic and/or portal veins indicates active or poorly controlled disease. Increased thrombosis may present in patients with PNH and aHUS who suspend treatment. Patients with underlying disease may still derive benefit from treatment with BEKEMV and the use of BEKEMV in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
History of bone marrow transplantation	Due to the mechanism of action, there is an increased risk for bacterial infections with ABP 959 and the reference medicinal product, Soliris.	No	In line with the reference medicinal product, Soliris, cautionary language concerning use in patients with active systemic infections is addressed in SmPC Section 4.4, Special warnings and precautions for use.
Red blood cell transfusion required within 12 weeks before randomization	To ensure that the evaluation of the safety and efficacy profile in clinical studies was not affected.	No	Patients with recent history of red blood cell transfusion may be an indication of recent breakthrough or poorly controlled disease. This risk is expected to be comparable to that of the reference medicinal product, Soliris. This restriction is not justified if treatment is prescribed to control the disease.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Subject experienced ≥ 2 breakthrough events, (ie, signs and symptoms of intravascular hemolysis, that require dose and/or schedule adjustments of eculizumab) in the previous 12 months before screening	To ensure that the evaluation of the safety and efficacy profile in clinical studies was not affected.	No	Patients with recent history of breakthrough events may be an indication of poorly controlled disease. This risk is expected to be comparable to that of the reference medicinal product, Soliris. This restriction is not justified if treatment is prescribed to control disease.

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SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program 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 Programs

Table 8. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Pregnant women were not included in the ABP 959 clinical development program. There are no well-controlled studies in pregnant women treated with Soliris; however, there are data on a limited number of pregnancies exposed to eculizumab (less than 300 pregnancy outcomes) that indicate there is no increased risk of fetal malformation or fetal-neonatal toxicity (Soliris SmPC).
Breastfeeding women	Breastfeeding women were not included in the ABP 959 clinical development program. No effects on the breastfed newborn/infant are anticipated as limited data available suggest that eculizumab is not excreted in human breast milk. However, due to the limitations of the available data, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for eculizumab and any potential adverse effects on the breastfed child from eculizumab or from the underlying maternal condition (Soliris SmPC).

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Table 8. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Patients with relevant comorbidities	
Patients with hepatic impairment	Not included in the ABP 959 clinical development program in line with the reference medicinal product, Soliris. The safety and efficacy of Soliris have not been studied in patients with hepatic impairment (Soliris SmPC).
Patients with renal impairment	Not included in the ABP 959 clinical development program. Patients with atypical hemolytic uremic syndrome and requiring dialysis were included in the reference medicinal product, Soliris, clinical development program (Soliris SmPC).
Patients with cardiovascular impairment	Subjects with clinically significant cardiovascular disease were excluded from the ABP 959 clinical development program. Exposure data for subjects with clinically significant cardiovascular disease in the Soliris clinical development program is unknown (Soliris SmPC).
Immunocompromised patients	Not included in the ABP 959 clinical development program. Exposure data for immunocompromised subjects in the Soliris clinical development program is unknown (Soliris SmPC).
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the ABP 959 clinical development program. Exposure data for subjects with a disease severity different from inclusion criteria in clinical trials in the Soliris clinical development program is unknown (Soliris SmPC).
Population with relevant different ethnic origin	ABP 959 and Soliris have been studied in subject populations of a variety of racial backgrounds and ethnicity in clinical studies (Table 6; Soliris SmPC).
Subpopulations carrying relevant genetic polymorphisms	Subjects with known or suspected hereditary complement deficiency were excluded from the ABP 959 clinical development program. Exposure data for subpopulations carrying relevant genetic polymorphisms in the Soliris clinical development program is unknown (Soliris SmPC).

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes), and in part on observed drug utilization parameters. Worldwide unit sales are recorded monthly by country and are converted to estimates of person time and when feasible, person count, using region- and product-specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

Postmarketing patient exposure estimates are reported overall and for Europe (EU, European Economic Area, Switzerland, and the United Kingdom), and Other (countries not otherwise specified).

Estimates of number of patients exposed and postmarketing patient exposure by age and sex are not yet available for BEKEMV.

SV.1.2 Exposure

Table 9. Estimated Number of Patient-years of Exposure to BEKEMV by Region, in the Postmarketing Setting Cumulatively Since Launch

	Cumulative Number of Patient-years of Exposure		
	EUR	Other	Total
Overall	297	16	313

EUR = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom); Other = countries not otherwise specified.
Note: Numbers may not add to the total due to rounding.
Cumulatively through 01 October 2024.

Postauthorization Use From Business Partners

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed in the clinical studies to date for ABP 959. The reference medicinal product, Soliris, is not associated with any abuse potential.

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

Although this is the initial RMP for BEKEMV, the risks not considered important for inclusion in the list of safety concerns in the RMP are not described here due to the lack of available data for the reference medicinal product. Please refer to the full safety profile in the SmPC for BEKEMV and the SmPC for the reference medicinal product, Soliris.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

BEKEMV is a biosimilar product, therefore the list of safety concerns considered important is aligned with that of the reference medicinal product, Soliris.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Table 10. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns		
Important Identified Risks		
Aspergillus Infection	*Aspergillus* Infection, previously classified as an important identified risk, has been removed from the list of safety concerns	This safety concern is removed to align with the reference medicinal product Soliris
Important Potential Risks		
Serious hemolysis after drug discontinuation in paroxysmal nocturnal hemoglobinuria patients	Serious hemolysis after drug discontinuation in paroxysmal nocturnal hemoglobinuria patients, previously classified as an important potential risk, has been removed from the list of safety concerns	This safety concern is removed to align with the reference medicinal product Soliris
Immunogenicity	Immunogenicity, previously classified as an important potential risk, has been removed from the list of safety concerns	This safety concern is removed to align with the reference medicinal product Soliris

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

No new safety concerns were identified in BEKEMV clinical program therefore the important identified risks and important potential risks presented for BEKEMV are presented as per the Soliris EU RMP with 1 exception: BEKEMV contains 50 mg sorbitol (E420) in each mL (as an excipient) and it is contraindicated in patients with hereditary fructose intolerance (HFI) regardless of their age, and in babies and children below 2 years of age, who may not yet be diagnosed with HFI. Serious and life-threatening effects may develop in patients with HFI due to their inability to metabolize intravenously administered sorbitol. As such, the important potential risk of serious metabolic harms due to sorbitol exposure in patients with HFI was added to the list of safety concerns for BEKEMV.

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 11. Important Identified Risk: Meningococcal Infections

Potential mechanisms	The eculizumab mode of action is based on terminal complement inhibition, 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, 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.
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medicinal product Soliris. Evidence sources: ABP 959 clinical study of PNH and Soliris SmPC.
Characterization of the risk	
Frequency	**ABP 959 study:** There were no adverse events of meningococcal infections[a] reported in the randomized, double-blind, active-controlled, 2-period crossover, phase 3 study evaluating the efficacy and safety of ABP 959 compared with eculizumab in adult subjects with PNH (Study 20150168). **Soliris studies:** Meningococcal infection, which also included meningococcal sepsis, meningitis meningococcal, and *Neisseria* infection, was reported as an uncommon adverse reaction in clinical trials and in the postmarketing setting. In all clinical studies, the most serious adverse reaction was meningococcal sepsis, which is a common presentation of meningococcal infections in patients treated with Soliris (Soliris SmPC).
Severity	No adverse events of meningococcal infections[a] were reported in Study 20150168. Severity data for ABP 959 are expected to be comparable to Soliris. Cases of serious or fatal meningococcal infections have been reported in Soliris-treated patients (Soliris SmPC).
Reversibility	Meningococcal infections may resolve with appropriate treatment. However, fatal outcomes have been reported in patients treated with Soliris (Soliris SmPC).
Long-term outcomes	Long-term outcome data are not available for BEKEMV, but are expected to be comparable to Soliris.
Impact on quality of life	Impact on quality of life would depend on the severity and nature of the symptoms.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 11. Important Identified Risk: Meningococcal Infections

Risk groups or risk factors	Risk factors for meningococcal 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 *Neisseria meningitidis* • Military personnel during recruit training (military personnel may be at increased risk of meningococcal infection when accommodated in close quarters) • Day-care center workers • Living on a college or university campus • Travelling to endemic areas for meningococcal meningitis (eg, 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	BEKEMV should not be initiated in patients with unresolved *Neisseria meningitidis* infection or who are not currently vaccinated against *Neisseria meningitidis*, unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. Vaccines against all available serogroups including A, C, Y, W 135, and B are recommended in preventing the commonly pathogenic meningococcal serogroups. Patients must be vaccinated and revaccinated according to current national guidelines for vaccination use. Patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. In addition, patients should be informed of the signs and symptoms of meningococcal infections and advised to seek medical care immediately if these are present. Additional risk minimization measures are provided to mitigate this risk, which include a guide for healthcare professionals, guide for patients/parents/caregivers, patient card, and annual vaccination reminder (see Part V.2 for details).
Impact on the risk-benefit balance of the product	The risk of meningococcal infections has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling and use of the guide for healthcare professionals, guide for patients/parents/caregivers, patient card, and annual vaccination reminder.
Public health impact	BEKEMV is indicated in a specific and limited population. Due to the relatively small number of patients exposed to the drug, the overall impact on public health is considered to be low. The public health impact is not expected to be greater than the reference medicinal product Soliris.

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aHUS = atypical hemolytic uremic syndrome; C5 = complement protein 5; PNH = paroxysmal nocturnal hemoglobinuria; SmPC = Summary of Product Characteristics

[a] For identification of potential events of meningococcal infections, the following search strategy was utilized: Neisseria infections High Level Term (HLT).

Table 12. Important Identified Risk: Serious Infections (Including Sepsis)

Potential mechanisms	The 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 comparing treated and untreated patients which do not demonstrate association between eculizumab treatment and infections other than *Neisseria spp.* infections.
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medicinal product Soliris. Evidence sources: ABP 959 clinical study of PNH and Soliris SmPC.
Characterization of the risk	
Frequency	**ABP 959 study:** In Study 20150168, the subject incidence of adverse events of serious infections[a] was 3 of 41 subjects (7.3%; 95% CI: 1.5, 19.9) while receiving ABP 959 treatment (preferred terms: gastroenteritis, COVID-19, and streptococcal urinary tract infection); there were no events reported in subjects while receiving eculizumab treatment. **Soliris studies:** Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported. Cases of *Neisseria* species included sepsis with *Neisseria gonorrhoeae*, *Neisseria sicca/subflava*, and *Neisseria spp.* unspecified. In clinical trials and in the postmarketing setting, sepsis and septic shock were reported as uncommon adverse reactions, and gonococcal infection was reported as a rare adverse reaction (Soliris SmPC).
Severity	In Study 20150168, the adverse events of serious infections[a] in subjects while receiving ABP 959 treatment were reported as moderate or severe; no events had a fatal outcome, all events were resolved without sequelae. Severity data for ABP 959 are expected to be comparable to Soliris.
Reversibility	Serious infections (including sepsis) may resolve with appropriate treatment.
Long-term outcomes	Long-term outcome data are not available for BEKEMV, but are expected to be comparable to Soliris.
Impact on quality of life	Impact on quality of life would depend on the severity and nature of the symptoms.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 12. Important Identified Risk: Serious Infections (Including Sepsis)

Risk groups or risk factors	Underlying immunodeficiency condition represents general risk factor for serious infection: either acquired (eg, aplastic anemia or myelodysplastic syndrome [MDS] in patients with PNH or end-stage renal disease in patients with aHUS) or due to other immunosuppressive drugs (eg, long-term use of corticosteroids and/or immunosuppressive agents).
Preventability	BEKEMV therapy should be administered with caution to patients with active systemic infections. 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. Patients should be informed of the signs and symptoms of potential serious infections and advised to seek urgent medical care if they suspect they have an infection. Physicians should also provide advice about gonorrhea prevention. All patients should follow regional vaccination recommendations, including children. Additional risk minimization measures are provided to mitigate this risk, which include a guide for patients/parents/caregivers and patient card (see Part V.2 for details).
Impact on the risk-benefit balance of the product	The risk of serious infections (including sepsis) has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling and use of the guide for patients/parents/caregivers and patient card.
Public health impact	BEKEMV is indicated in a specific and limited population. Due to the relatively small number of patients exposed to the drug, the overall impact on public health is considered to be low. The public health impact is not expected to be greater than the reference medicinal product, Soliris.

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aHUS = atypical hemolytic uremic syndrome; C5 = complement protein 5; MDS = myelodysplastic syndrome; PNH = paroxysmal nocturnal hemoglobinuria; SmPC = Summary of Product Characteristics

[a] For identification of potential events of serious infections (including sepsis), the following search strategy was utilized: Infections and infestations System Organ Class, limited to adverse events Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher and serious adverse events.

Table 13. Important Identified Risk: Severe TMA Complications due to Drug Discontinuation in aHUS Patients

Potential mechanisms	Atypical hemolytic uremic syndrome 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 important identified risk is included per the reference medicinal product Soliris. Evidence source: Soliris SmPC.
Characterization of the risk	
Frequency	**ABP 959 study:** Not applicable. **Soliris studies:** In aHUS clinical studies 61 patients (21 paediatric patients) discontinued Soliris treatment with a median follow-up period of 24 weeks. Fifteen severe TMA complications in 12 patients were observed following treatment discontinuation, and 2 severe TMA complications occurred in an additional 2 patients that received a reduced dosing regimen of Soliris outside of the approved dosing regimen (Soliris SmPC).
Severity	Severity data for ABP 959 are expected to be comparable to Soliris.
Reversibility	In Soliris studies, despite Soliris re-initiation following discontinuation, progression to end stage renal disease occurred in 1 patient
Long-term outcomes	Long-term outcome data are not available for BEKEMV, but are expected to be comparable to Soliris.
Impact on quality of life	Impact on quality of life would depend on the severity and nature of the symptoms. Long-term treatment may be required for severe TMA complications due to drug discontinuation in aHUS patients.
Risk groups or risk factors	Complement dysregulation in patients with aHUS due to genetic abnormalities or acquired deficiencies is associated with TMA represent known risk factors.
Preventability	Discontinuation of treatment should only be considered if medically justified. Healthcare professionals (HCPs) should closely monitor aHUS patients who discontinue treatment with BEKEMV for signs and symptoms of severe TMA complications. A guide for patients/parents/caregivers is provided to mitigate this risk (see Part V.2 for details).

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 13. Important Identified Risk: Severe TMA Complications due to Drug Discontinuation in aHUS Patients

Impact on the risk-benefit balance of the product	The risk of severe TMA complications due to drug discontinuation in aHUS patients has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling and use of the guide for patients/parents/caregivers.
Public health impact	BEKEMV is indicated in a specific and limited population. Due to the relatively small number of patients exposed to the drug, the overall impact on public health is considered to be low. The public health impact is not expected to be greater than the reference medicinal product Soliris.

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aHUS = atypical hemolytic uremic syndrome; C5 = complement protein 5; HCP = healthcare professional; SmPC = Summary of Product Characteristics; TMA = thrombotic microangiopathy complications

Table 14. Important Identified Risk: Infusion Reactions

Potential mechanisms	As with all therapeutic proteins, administration of BEKEMV may result in infusion reactions and could cause allergic or hypersensitivity reactions. The underlying mechanism in the majority of infusion reactions may be related to immunological and non-immunological mechanisms and the formation of antidrug antibodies (ADAs). In line with the Soliris RMP, administration of BEKEMV may result in infusion reactions and could cause allergic or hypersensitivity reactions. Most of the infusion reactions that occurred in patients receiving eculizumab were nonserious and did not require discontinuation of eculizumab. In the postmarketing setting, anaphylactic/anaphylactoid reactions have been reported during or following eculizumab infusion.
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medicinal product Soliris. Evidence sources: ABP 959 clinical study of PNH and Soliris SmPC.
Characterization of the risk	
Frequency	**ABP 959 study:** In Study 20150168, no subjects reported the preferred term infusion-related reaction while on study. The subject incidence of retrieved adverse events of infusion reactions per event of interest (EOI) search strategy[a] was 15 of 41 subjects (36.6%; 95% CI: 22.1, 53.1) while receiving ABP 959 treatment and 15 of 42 subjects (35.7%; 95% CI: 21.6, 52.0) while receiving eculizumab treatment. Through the end of study, the most frequently reported preferred terms (≥ 5%) with ABP 959 treatment included fatigue (4 of 41 subjects, or 9.8%) and pruritus (3 of 41 subjects, or 7.3%). **Soliris studies:** In clinical trials and in the postmarketing setting, infusion related reaction, anaphylactic reaction, and hypersensitivity were reported as uncommon adverse reactions (Soliris SmPC).
Severity	In Study 20150168, all retrieved adverse events of infusion reactions per EOI search strategy[a] reported in subjects while receiving ABP 959 treatment were mild or moderate in severity, which was comparable with the events reported in subjects while receiving eculizumab treatment; no events had a fatal outcome. Over the entire study, 1 subject presented transient Common Terminology Criteria for Adverse Events (CTCAE) grade 2 eye pruritus and CTCAE grade 2 flushing while receiving ABP 959 infusion, requiring a partial dose administration and intravenous antihistamine treatment. The symptoms did not recur with further ABP 959 infusion administrations. Anaphylaxis is a severe hypersensitivity reaction. In clinical trials, 1 (0.9%) generalized myasthenia gravis patient experienced an infusion reaction which required discontinuation of Soliris. No PNH or aHUS patients experienced an infusion reaction which required discontinuation of Soliris (Soliris SmPC).

Footnotes, including abbreviations, are defined on the last page of the table.

Table 14. Important Identified Risk: Infusion Reactions

Characterization of the risk (continued)	
Reversibility	Infusion reactions may be reversible upon discontinuation of BEKEMV and administration of appropriate treatment.
Long-term outcomes	Long-term outcome data are not available for BEKEMV, but are expected to be comparable to Soliris.
Impact on quality of life	Impact on quality of life would depend on the severity and nature of the symptoms.
Risk groups or risk factors	Patients with hypersensitivity to eculizumab or to any of the excipients. No data were identified for the risk factors for infusion reactions in patients with PNH or aHUS.
Preventability	BEKEMV therapy should not be administered to patients with hypersensitivity to eculizumab or to any of the excipients listed in the SmPC. Instructions for dilution and length of infusion administration are to be followed as described in Section 4.2 of the SmPC. Following an infusion of BEKEMV, patients should be monitored for 1 hour. BEKEMV administration should be interrupted in all patients experiencing severe infusion reactions and appropriate medical therapy should be administered.
Impact on the risk-benefit balance of the product	The risk of infusion reactions has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling.
Public health impact	BEKEMV is indicated in a specific and limited population. Due to the relatively small number of patients exposed to the drug, the overall impact on public health is considered to be low. The public health impact is not expected to be greater than the reference medicinal product Soliris.

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ADA = antidrug antibody; aHUS = atypical hemolytic uremic syndrome; CTCAE = Common Terminology Criteria for Adverse Events; EOI = event of interest; PNH = paroxysmal nocturnal hemoglobinuria; SmPC = Summary of Product Characteristics

[a] For identification of potential infusion reaction events of interest, the following search strategy was utilized: Infusion reaction Amgen Medical Dictionary for Regulatory Activities (MedDRA) Query (broad scope) and Hypersensitivity Standardized Medical Dictionary for Regulatory Activities Query (SMQ; broad scope), limited to events that occur with start date same as or 1 day after investigational product administration start date.

Table 15. Important Potential Risk: Serious Metabolic Harms Due to Sorbitol Exposure in Patients With Hereditary Fructose Intolerance

Potential mechanisms	Sorbitol, an excipient of BEKEMV, is rapidly converted in vivo to fructose by sorbitol dehydrogenase in the liver; therefore, systemic safety concerns regarding fructose also apply to sorbitol. Hereditary fructose intolerance (HFI) is a hereditary autosomal recessive disorder with a worldwide incidence at birth estimated at 1:20 000 to 1:30 000. HFI presents a deficit in fructose 1,6-bisphosphate aldolase (aldolase B), the main enzyme responsible for hepatic metabolism of fructose. It is expressed in the liver, small intestine, and proximal renal tubule where it facilitates assimilation of dietary fructose by catalyzing the cleavage of fructose-1-phosphate. A lack of functional aldolase B leads to an accumulation of toxic fructose 1-phosphate in liver cells, ultimately resulting in hepatic decompensation. Patients with HFI develop a natural defense mechanism against fructose and sorbitol by vomiting any food containing either of the 2 substances. Since this defense mechanism is bypassed when fructose or sorbitol is delivered intravenously, a much higher risk is associated with solutions for parenteral (especially intravenous) use (Steinmann et al, 2019; EMA, 2017; Cox, 1990).
Evidence source(s) and strength of evidence	This is considered an important potential risk based on the known effects of administering other parenteral sorbitol/fructose-containing medicines to patients with HFI. Babies and children below 2 years of age represent a population with high risk, as HFI may not yet have been diagnosed (EMA, 2017). BEKEMV is contraindicated in patients with HFI (regardless of their age), and in babies and children below 2 years of age.
Characterization of the risk	
Frequency	**ABP 959 study:** Not studied; children and subjects with HFI were not included in Study 20150168. **Soliris studies:** Not applicable.
Severity	Serious metabolic harms including life-threatening and fatal events have been reported in the literature. Metabolic disturbances including hypoglycemia, lactic acidemia, hypophosphatemia, hyperuricemia, hypermagnesemia, and hyperalaninemia may develop, and lethargy, seizures, or progressive coma may present (Gaughan et al, 2021; Cox, 1993; Cox, 1990).
Reversibility	Fatal events have been reported in the literature. Severe and life-threatening events may require hospital admission or intensive care, due to the various metabolic abnormalities triggered by the sorbitol/fructose exposure. Adequate supportive treatment may re-establish metabolic homeostasis, depending upon the severity of the presenting symptoms (Gaughan et al, 2021; Cox, 1993; Cox, 1990).

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 15. Important Potential Risk: Serious Metabolic Harms Due to Sorbitol Exposure in Patients With Hereditary Fructose Intolerance

Characterization of the risk (continued)	
Long-term outcomes	No data are available.
Impact on quality of life	If sorbitol/fructose-containing infusions are given to patients with HFI, acute metabolic derangements and hepatic and renal insufficiency can develop, followed by death within a few days (EMA, 2017).
Risk groups or risk factors	Patients diagnosed with HFI (regardless of their age), and babies and children below 2 years of age with potentially undiagnosed HFI. The worldwide incidence of HFI at birth is estimated at 1:20 000 to 1:30 000. The disorder is not apparent until the infant is weaned and fed with formula, juice, fruits, baby foods, or honey that contain fructose. In young children, a spontaneous aversion for fructose develops and the onset of symptoms may be delayed when parents scrupulously respect the child's tastes for food and do not impose fructose-containing products rejected by the child (EMA, 2017). Chronically untreated exposure to sorbitol in patients with HFI may result in failure to thrive and renal and hepatic failure (Gaughan et al, 2021; Steinmann et al, 2019).
Preventability	BEKEMV must not be given to patients with HFI (regardless of their age), or to babies and children below 2 years of age. Additional risk minimization measures are provided to mitigate this risk, which include a guide for healthcare professionals, guide for patients/parents/caregivers, and patient card (see Part V.2 for details), as well as routine risk minimization measures including a visual reminder of sorbitol content and risk of sorbitol exposure in patients with HFI in the product outer packaging.
Impact on the risk-benefit balance of the product	The risk of serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labeling, product packaging, and use of the guide for healthcare professionals, guide for patients/parents/caregivers, and patient card.
Public health impact	BEKEMV is indicated in a specific and limited population. The coexistence of HFI with PNH or aHUS (the indications for BEKEMV) is expected to be very rare. Due to the anticipated small number of PNH and aHUS patients with HFI, the overall impact on public health is considered to be low.

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aldolase B = fructose 1,6-bisphosphate aldolase; aHUS = atypical hemolytic uremic syndrome; EMA = European Medicines Agency; HFI = hereditary fructose intolerance; PNH = paroxysmal nocturnal hemoglobinuria

SVII.3.2 Presentation of the Missing Information

Not applicable.

Part II: Module SVIII – Summary of the Safety Concerns

Table 16. Summary of Safety Concerns

Important identified risks	• Meningococcal infections • Serious infections (including sepsis) • Severe TMA complications due to drug discontinuation in aHUS patients • Infusion reactions
Important potential risks	• Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance
Missing information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 17.

Table 17. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Meningococcal infection questionnaire	Meningococcal infections	To further characterize events of meningococcal infection reported in patients treated with BEKEMV in the postmarketing environment.

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance activities.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned BEKEMV category 1 to 3 studies.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

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

Risk Minimization Plan

The safety information in the proposed BEKEMV SmPC is aligned to the reference medicinal product, Soliris.

V.1 Routine Risk Minimization Measures

Table 18. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Meningococcal infections	Routine risk communication: • SmPC Sections 4.3, 4.4, and 4.8 • Package leaflet (PL) Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Contraindication in patients with unresolved *Neisseria meningitidis* infection or without vaccination/antibiotic prophylaxis is included in SmPC Section 4.3. • Recommendation for Vaccination (including the need for antibiotic prophylaxis until 2 weeks after vaccination for patients who initiate BEKEMV treatment less than 2 weeks after vaccination) and monitoring patients for meningococcal infection is recommended in SmPC Section 4.4. • Information on educational materials is included in SmPC Section 4.4 • Signs and symptoms of meningococcal infections are listed in SmPC Section 4.4 and PL Section 2. Other risk minimization measures beyond the PI: • Restricted medical prescription
Serious infections (including sepsis)	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to inform patients of the signs and symptoms of potential serious infections and to provide advice about gonorrhea prevention is included in SmPC Section 4.4. Other risk minimization measures beyond the PI: • Restricted medical prescription

Table 18. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (continued)	
Severe TMA complications due to drug discontinuation in aHUS patients	Routine risk communication: • SmPC Sections 4.2 and 4.4 • PL Section 3 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to monitor patients with aHUS for signs and symptoms of TMA is included in SmPC Section 4.2. • Recommendation to monitor patients who discontinued BEKEMV is included in SmPC Section 4.4 and PL Section 3 • Recommendation to reinstate BEKEMV therapy and administer appropriate medical therapy if severe TMA complications occur is included in SmPC Section 4.4 Other risk minimization measures beyond the PI: • Restricted medical prescription
Infusion reactions	Routine risk communication: • SmPC Sections 4.2, 4.4, and 4.8 • PL Section 2, 3, and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to monitor patients for 1 hour following infusion is included in SmPC Section 4.2 • Recommendation to interrupt administration of BEKEMV and administer appropriate medical therapy if a patient experiences a severe infusion reaction is included in SmPC Section 4.4 Other risk minimization measures beyond the PI: • Restricted medical prescription

Table 18. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks	
Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance	Routine risk communication: • SmPC Sections 2, 4.2, 4.3, 4.4, and 6.1 • PL Sections 2, 3, and 6 • Outer packaging Sections 3 and 7 Routine risk minimization activities recommending specific clinical measures to address the risk: • Contraindication in patients with HFI is included in SmPC Sections 4.3 and 4.4, and PL Section 2. • Contraindication in babies and children below 2 years of age, who may not yet be diagnosed with HFI, is included in SmPC Sections 4.2, 4.3, and 4.4, and PL Section 2. • Recommendation to take a detailed history of each patient with regards to HFI symptoms prior to receiving BEKEMV and immediately stop BEKEMV infusion in case of inadvertent administration and suspicion of fructose intolerance, re-establish normal blood glucose levels, and stabilize organ function by means of intensive care, is included in SmPC Section 4.4. Other risk minimization measures beyond the PI: • Restricted medical prescription
Missing Information	
None	

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V.2 Additional Risk Minimization Measures

Table 19. Additional Risk Minimization Measure: Guide for Healthcare Professionals

Objectives	To instruct HCPs about the detection, careful monitoring, and proper management of meningococcal infections associated with BEKEMV. To educate HCPs about *Neisseria meningitidis* vaccines: to instruct HCPs regarding re-vaccination according to manufacturers' direction through product information and national guidelines/recommendations. To have all patients vaccinated at least 2 weeks prior to receiving BEKEMV unless the risk of delaying BEKEMV 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 2 weeks prior to receiving BEKEMV must receive prophylactic antibiotics before and until 2 weeks after the vaccination. To instruct HCPs on BEKEMV contraindication in patients with HFI (regardless of their age), and in babies and children below 2 years of age, who may not yet be diagnosed with HFI, and to inform them of the presence of sorbitol in BEKEMV and the risk of serious metabolic harms due to sorbitol exposure in patients with HFI. List of addressed safety concerns: • Meningococcal infections • Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance
Rationale for the additional risk minimization activity	This additional risk minimization activity is proposed to align with the reference medicinal product, Soliris, to inform HCPs regarding the risk of meningococcal infection associated with eculizumab treatment, that may lead to a fatal outcome. Healthcare professionals must educate their patients to seek immediate medical care as soon as they experience any signs and symptoms of meningococcal infections. In addition, to inform HCPs about BEKEMV contraindication in patients with HFI (regardless of their age), and in babies and children below 2 years of age, who may not yet be diagnosed with HFI, and the risk of intravenous sorbitol administration to patients with HFI with the development of severe metabolic abnormalities and life-threatening symptoms including hypoglycemia, metabolic acidosis, seizures, and coma. Healthcare professionals must educate their patients on these risks and obtain a family history of HFI and a detailed history of their dietary habits before starting treatment with BEKEMV.

Table 19. Additional Risk Minimization Measure: Guide for Healthcare Professionals

Target audience and planned distribution path	All HCPs prescribing BEKEMV.
Plans to evaluate the effectiveness of the interventions and criteria for success	The effectiveness of the Guide for Healthcare Professionals will be assessed using routine pharmacovigilance including monthly signal detection and reporting in scheduled Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR) or earlier, if required.
Evaluation of the effectiveness of risk minimization activities	Not yet assessed.

Table 20. Additional Risk Minimization Measure: Guide for Patients/Parents/Caregivers

Objectives	To educate patients/parents/caregivers about the detection and proper management of selected safety concerns associated with BEKEMV. To have all patients vaccinated at least 2 weeks prior to receiving BEKEMV unless the risk of delaying BEKEMV 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 2 weeks prior to receiving BEKEMV must receive prophylactic antibiotics before and until 2 weeks after the vaccination. To instruct patients/parents/caregivers about the detection of possible meningococcal or general infection and steps to manage based on product information. To instruct patients and pediatric patients' parent(s)/legal guardian(s) on BEKEMV contraindication in patients with HFI (regardless of their age), and in babies and children below 2 years of age, who may not yet be diagnosed with HFI and to inform them of the presence of sorbitol in BEKEMV and the risk of serious metabolic harms due to sorbitol exposure in patients with HFI. List of addressed safety concerns: • Meningococcal infections • Serious infections (including sepsis) • Severe TMA complications due to drug discontinuation in aHUS patients • Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance
Rationale for the additional risk minimization activity	This additional risk minimization activity is proposed to align with the reference medicinal product, Soliris, to inform patients/parents/caregivers about the main risks associated with eculizumab treatment, especially the risk of meningococcal infections associated with eculizumab treatment that may lead to a fatal outcome. Patients/parents/caregivers 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 times. In addition, to inform patients and the parent(s)/legal guardian(s) of pediatric patients about the contraindication to patients with HFI (regardless of their age), and to babies and children below 2 years of age, who may not yet be diagnosed with HFI. And the risk of intravenous sorbitol exposure in patients with HFI, with the development of severe and life-threatening symptoms (including seizures and coma). Patients and the parent(s)/legal guardian(s) of pediatric patients must discuss their family history of HFI and a detailed history of their dietary habits before starting treatment with BEKEMV.

Table 20. Additional Risk Minimization Measure: Guide for Patients/Parents/Caregivers

Target audience and planned distribution path	• Patients • Physicians other than the usual prescribers • Parents, caregivers, and other child carers (eg, school, day care services or persons, etc.)
Plans to evaluate the effectiveness of the interventions and criteria for success	The effectiveness of the Guide for Patients/Parents/Caregivers will be assessed using routine pharmacovigilance including monthly signal detection and reporting in scheduled PBRER/PSUR or earlier, if required.
Evaluation of the effectiveness of risk minimization activities	Not yet assessed.

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Table 21. Additional Risk Minimization Measure: Patient Card

Objectives	To list signs and symptoms of meningococcal infections to help patients/parents/caregivers to identify potential meningococcal infection and to seek immediately medical care. When patients present to an HCP different than the usual prescriber, it helps to promptly identify potential meningococcal infection and to initiate appropriate antibiotic treatment. In addition, to inform patients or their parents/legal guardians or other child carers of BEKEMV contraindication in patients with HFI (regardless of their age), and in babies and children below 2 years of age, who may not yet be diagnosed with HFI and to inform them of the presence of sorbitol in BEKEMV and the risk of serious metabolic harms due to sorbitol exposure in patients with HFI. It also provides information to the HCP different than the usual prescriber regarding the metabolic abnormalities and life-threatening symptoms that patients with HFI may present subsequent to sorbitol administration. List of addressed safety concerns: • Meningococcal infections • Serious infections (including sepsis) • Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance
Rationale for the additional risk minimization activity	This additional risk minimization activity is proposed to align with the reference medicinal product, Soliris. Signs and symptoms of meningococcal infections need to be recognized in a timely manner. This card highlights these signs and symptoms as well as the need for seeking immediate medical attention if they occur. The card also emphasizes that the patient must receive vaccination or revaccination according to current national vaccination guidelines for vaccination use. In addition to the reference product material, patients are warned about BEKEMV contraindication in patients with HFI (regardless of their age), and in babies and children below 2 years of age, who may not yet be diagnosed with HFI and the risks (potentially life-threatening) when exposed to sorbitol-containing medicines. Healthcare professionals are informed of symptoms that patients with HFI may present if intravenously exposed to sorbitol, including hypoglycemia, metabolic acidosis, seizures, coma, and to treat immediately if HFI is suspected.
Target audience and planned distribution path	• Patients/parents/caregivers • Physicians other than usual prescribers.
Plans to evaluate the effectiveness of the interventions and criteria for success	The effectiveness of the Patient Card will be assessed using routine pharmacovigilance including monthly signal detection and reporting in scheduled PBRER/PSUR or earlier, if required.
Evaluation of the effectiveness of risk minimization activities	Not yet assessed.

Table 22. Additional Risk Minimization Measure: Annual Vaccination Reminders for Healthcare Professionals

Objectives	To remind HCPs on an annual basis to verify and ensure that the patients vaccination against meningococcal infection are still current according to local vaccination guideline. List of addressed safety concerns: • Meningococcal infections
Rationale for the additional risk minimization activity	This additional risk minimization activity is proposed to align with the reference medicinal product, Soliris, to highlight the importance of an effective vaccination against meningococcal infection to minimize this important risk.
Target audience and planned distribution path	Prescribers or pharmacists who prescribe/dispense eculizumab.
Plans to evaluate the effectiveness of the interventions and criteria for success	The marketing authorization holder (MAH) ensures the reminder is sent annually to the HCPs.
Evaluation of the effectiveness of risk minimization activities	Not yet assessed.

Table 23. Removal of Additional Risk Minimization Activities

Additional Risk Minimization Activities Proposed to be Removed	Rationale for the Removal
Controlled Distribution	This additional risk minimization measure is removed to align with the reference medicinal product, Soliris. The revised additional risk minimization measures will consist of a guide for HCPs, a guide for patients/parents/caregivers, and a patient card. The annual vaccination reminders will continue to be sent to HCPs.

V.3 Summary of Risk Minimization Measures

Table 24. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Meningococcal infections	Routine risk minimization measures: • SmPC Section 4.3 where a contraindication is included • SmPC Section 4.4 where recommendation for vaccination (including the need for antibiotic prophylaxis until 2 weeks after vaccination for patients who initiate BEKEMV treatment less than 2 weeks after vaccination), information on educational materials, and monitoring for meningococcal infection are included and where signs and symptoms of meningococcal infections are listed • SmPC Section 4.8 • PL Section 2 where signs and symptoms of meningococcal infections are listed • PL Section 4 • Restricted medical prescription Additional risk minimization measures: • Guide for healthcare professionals • Guide for patients/parents/caregivers • Patient card • Annual vaccination reminders for healthcare professionals	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 minimization measures: • SmPC Section 4.4 where recommendation to inform patients of the signs and symptoms of potential serious infections and to advise patients about gonorrhea prevention is included • SmPC Section 4.8 • PL Sections 2 and 4 • Restricted medical prescription Additional risk minimization measures: • Guide for patients/parents/caregivers • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Table 24. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Severe TMA complications due to drug discontinuation in aHUS patients	Routine risk minimization measures: • SmPC Section 4.2 where recommendations to monitor patients with aHUS for signs and symptoms of TMA and to monitor patients who discontinued BEKEMV are included. • SmPC Section 4.4 where a recommendation to monitor patients who discontinued BEKEMV, reinstate BEKEMV therapy and administer appropriate medical therapy if severe TMA complications occur is included • PL Section 3 where a recommendation to monitor patients who discontinued BEKEMV is included. • Restricted medical prescription Additional risk minimization measures: • Guide for patients/parents/caregivers	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Infusion reactions	Routine risk minimization measures: • SmPC Section 4.2 where a recommendation to monitor patients for 1 hour following infusion is included • SmPC Section 4.4 where a recommendation to interrupt administration of BEKEMV and administer appropriate medical therapy is included • SmPC Section 4.8 • PL Sections 2, 3, and 4 • Restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Table 24. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance	Routine risk minimization measures: • SmPC Section 2 • SmPC Section 4.2 where a contraindication in babies and children below 2 years of age, who may not yet be diagnosed with HFI, is included • SmPC Section 4.3 where a contraindication in patients with HFI and babies and children below 2 years of age, who may not yet be diagnosed with HFI, is included • SmPC Section 4.4 where a contraindication in patients with HFI and babies and children below 2 years of age, who may not yet be diagnosed with HFI, is included, and where a recommendation to take a detailed history of each patient with regards to HFI symptoms prior to receiving BEKEMV and immediately stop BEKEMV infusion in case of inadvertent administration and suspicion of fructose intolerance, re-establish normal blood glucose levels, and stabilize organ function by means of intensive care, is included • SmPC Section 6.1 • PL Section 2, where a contraindication in patients with HFI and babies and children below 2 years of age, who may not yet be diagnosed with HFI, is included • PL Section 3 • PL Section 6 • Outer packaging Sections 3 and 7 • Restricted medical prescription Additional risk minimization measures: • Guide for healthcare professionals • Guide for patients/parents/caregivers • Patient card • Additional national measures in alignment with national requirements for drug prescription, preparation, dispensing, and administration, if deemed necessary	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

A summary of the RMP for BEKEMV is presented below.

Summary of Risk Management Plan for BEKEMV (eculizumab)

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

BEKEMV's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how BEKEMV should be used.

This summary of the RMP for BEKEMV should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 BEKEMV's RMP.

I. The Medicine and What it is Used For

BEKEMV is indicated in adults and children for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) (see SmPC for the full indications). It contains eculizumab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of BEKEMV's benefits can be found in BEKEMV's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/bekemv.

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of BEKEMV, together with measures to minimize such risks and the proposed studies for learning more about BEKEMV's risks, are outlined below.

Measures to minimize 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 healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized 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 public (eg, with or without prescription) can help to minimize its risks.

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

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) 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 BEKEMV are risks that need special risk management activities to further investigate or minimize 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 BEKEMV. 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 (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Meningococcal infections • Serious infections (including sepsis) • Severe TMA complications due to drug discontinuation in aHUS patients • Infusion reactions
Important potential risks	• Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance
Missing information	• None

II.B. Summary of Important Risks

Important identified risk: Meningococcal infections	
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Soliris. Evidence sources: ABP 959 clinical study of PNH and Soliris SmPC.
Risk factors and risk groups	Risk factors for meningococcal 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 *Neisseria meningitidis* • Military personnel during recruit training (military personnel may be at increased risk of meningococcal infection when accommodated in close quarters) • Day-care center workers • Living on a college or university campus • Travelling to endemic areas for meningococcal meningitis (eg, 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 minimization measures	Routine risk minimization measures: • SmPC Section 4.3 where a contraindication is included • SmPC Section 4.4 where recommendation for vaccination (including the need for antibiotic prophylaxis until 2 weeks after vaccination for patients who initiate BEKEMV treatment less than 2 weeks after vaccination), information on educational materials, and monitoring for meningococcal infection are included and where signs and symptoms of meningococcal infections are listed • SmPC Section 4.8 • PL Section 2 where signs and symptoms of meningococcal infections are listed • PL Section 4 • Restricted medical prescription Additional risk minimization measures: • Guide for healthcare professionals • Guide for patients/parents/caregivers • Patient card • Annual vaccination reminder for healthcare professionals

Important identified risk: Serious infections (including sepsis)	
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Soliris. Evidence sources: ABP 959 clinical study of PNH and Soliris SmPC.
Risk factors and risk groups	Underlying immunodeficiency condition represents general risk factor for serious infection: either acquired (eg, aplastic anemia, myelodysplastic syndrome in patients with PNH, or end-stage renal disease in patients with aHUS) or due to other immunosuppressive drugs (eg, long-term use of corticosteroids and/or immunosuppressive agents).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where recommendation to inform patients of the signs and symptoms of potential serious infections and to advise patients about gonorrhea prevention is included • SmPC Section 4.8 • PL Sections 2 and 4 • Restricted medical prescription Additional risk minimization measures: • Guide for patients/parents/caregivers • Patient card

Important identified risk: Severe TMA complications due to drug discontinuation in aHUS patients	
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Soliris. Evidence source: Soliris SmPC.
Risk factors and risk groups	Complement dysregulation in patients with aHUS due to genetic abnormalities or acquired deficiencies is associated with TMA represent known risk factors.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 where recommendations to monitor patients with aHUS for signs and symptoms of TMA and to monitor patients who discontinued BEKEMV are included. • SmPC Section 4.4 where a recommendation to monitor patients who discontinued BEKEMV, reinstate BEKEMV therapy and administer appropriate medical therapy if severe TMA complications occur is included • PL Section 3 where a recommendation to monitor patients who discontinued BEKEMV is included. • Restricted medical prescription Additional risk minimization measures: • Guide for patients/parents/caregivers

Important identified risk: Infusion reactions	
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Soliris. Evidence sources: ABP 959 clinical study of PNH and Soliris SmPC.
Risk factors and risk groups	Patients with hypersensitivity to eculizumab or to any of the excipients. No data were identified for the risk factors for infusion reactions in patients with PNH or aHUS.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 where a recommendation to monitor patients for 1 hour following infusion is included • SmPC Section 4.4 where a recommendation to interrupt administration of BEKEMV and administer appropriate medical therapy is included • SmPC Section 4.8 • PL Sections 2, 3, and 4 • Restricted medical prescription Additional risk minimization measures: • None

Important potential risk: Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance	
Evidence for linking the risk to the medicine	This is considered an important potential risk based on the known effects of administering other parenteral sorbitol/fructose-containing medicines to patients with hereditary fructose intolerance. Babies and children below 2 years of age represent a population with high risk, as hereditary fructose intolerance may not yet have been diagnosed (European Medicines Agency: Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use; EMA/CHMP/460886/2014). BEKEMV is contraindicated in patients with hereditary fructose intolerance (regardless of their age), and in babies and children below 2 years of age.
Risk factors and risk groups	Patients diagnosed with hereditary fructose intolerance (regardless of their age), and babies and children below 2 years of age with potentially undiagnosed hereditary fructose intolerance. The worldwide incidence of hereditary fructose intolerance at birth is estimated at 1:20 000 to 1:30 000. The disorder is not apparent until the infant is weaned and fed with formula, juice, fruits, baby foods, or honey that contain fructose. In young children, a spontaneous aversion for fructose develops and the onset of symptoms may be delayed when parents scrupulously respect the child's tastes for food and do not impose fructose-containing products rejected by the child (European Medicines Agency: Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use; EMA/CHMP/460886/2014). Chronically untreated exposure to sorbitol in patients with hereditary fructose intolerance may result in failure to thrive and renal and hepatic failure.

Important potential risk: Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (continued)	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 2 • SmPC Section 4.2 where a contraindication in babies and children below 2 years of age, who may not yet be diagnosed with hereditary fructose intolerance, is included • SmPC Section 4.3 where a contraindication in patients with hereditary fructose intolerance and in babies and children below 2 years of age, who may not yet be diagnosed with hereditary fructose intolerance, is included • SmPC Section 4.4 where a contraindication in patients with hereditary fructose intolerance and in babies and children below 2 years of age, who may not yet be diagnosed with hereditary fructose intolerance is included, and where a recommendation to take a detailed history of each patient with regards to hereditary fructose intolerance symptoms prior to receiving BEKEMV and immediately stop BEKEMV infusion in case of inadvertent administration and suspicion of fructose intolerance, re-establish normal blood glucose levels, and stabilize organ function by means of intensive care, is included • SmPC Section 6.1 • PL Section 2, where a contraindication in patients with HFI and babies and children below 2 years of age, who may not yet be diagnosed with hereditary fructose intolerance, is included • PL Section 3 • PL Section 6 • Outer packaging Sections 3 and 7 • Restricted medical prescription Additional risk minimization measures: • Guide for healthcare professionals • Guide for patients/parents/caregivers • Patient card • Additional national measures in alignment with national requirements for drug prescription, preparation, dispensing, and administration, if deemed necessary

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II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of BEKEMV.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for BEKEMV.

PART VII: ANNEXES

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Annex 1. EudraVigilance Interface

Not applicable.

Annex 2. Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Not applicable.

Annex 3. Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

Not applicable.

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

Follow-up Form Title	Date of Follow-up Version
Meningococcal infection questionnaire	14 July 2022

AMGEN®

MENINGOCOCCAL INFECTION QUESTIONNAIRE

AER #

1. PATIENT INFORMATION (Please indicate dates as dd/mm/yyyy)

Patient Initials (Confidential)

Age at time of event

Gender ☐ Male ☐ Female

Date of birth

Weight _____ lb _____ kg

Race _____

Event(s) start date (dd/mm/yyyy)

Date of this report (dd/mm/yyyy)

2. MEDICATION ADMINISTERED (Please indicate dates as dd/mm/yyyy)

Amgen Drug

Dose | Frequency | Route

Date when first dose of Amgen drug was administered _____

Date when Amgen drug was most recently administered, before the event developed _____

Co-suspect medications (include start date) _____

Other concomitant medications _____

Was the Amgen drug Patient Safety Card presented to HCPs during the process of the patient seeking treatment for the event? ☐ Yes ☐ No _____

3. SIGNS AND SYMPTOMS (check all that apply, provide dates of onset/resolution if available as dd/mm/yyyy)

☐ Fever _____ ☐ Vomiting _____ ☐ Altered consciousness _____

☐ Headache _____ ☐ Photophobia _____ ☐ Cardio-respiratory impairment _____

☐ Rash _____ ☐ Abdominal pain _____ ☐ Other (specify) _____

☐ Stiff neck _____ ☐ Diarrhea _____ Infants/children may also present: ☐ Refusing to eat _____

☐ Arthralgia/Myalgia _____ ☐ Confusion _____ ☐ Irritability _____ ☐ Uncontrollable high pitch crying _____

☐ Nausea _____ ☐ Drowsiness _____ ☐ Lethargy _____ ☐ Floppiness _____ ☐ Seizures _____

4. PATIENT HISTORY AND RISK FACTORS FOR MENINGOCOCCAL INFECTION

What is the medical condition for which Amgen drug was prescribed? _____

Duration of medical condition for which Amgen drug was prescribed _____

Does the patient have any other chronic medical conditions? (Please specify, provide duration since diagnosis) _____

Does the patient have a history of (check all that apply):

☐ Functional or anatomic asplenia _____ ☐ HIV infection _____

☐ Immunosuppression _____ ☐ Prior history of meningococcal infection _____

☐ Genetic deficiency for complement components _____ ☐ Recent exposure to a meningococcal infection outbreak _____

☐ Professionals who are exposed to environments of greater risk for meningococcal disease _____

☐ Research, industrial, and clinical laboratory personnel who are routinely exposed to *Neisseria meningitidis* _____

☐ Military personnel during recruit training (may be at increased risk of meningococcal infection when accommodated in close quarters) _____

☐ Day-care center 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 Haj) _____

☐ Recent visit from people from endemic areas for meningococcal meningitis _____

☐ Other (please specify) _____

5. MENINGOCOCCAL VACCINATION STATUS AND ANTIBIOTIC PROPHYLAXIS

Was patient vaccinated against meningococcal infection before starting Amgen drug treatment? ☐ Yes ☐ No

If patient was vaccinated:

Name of vaccine _____

Date of most recent meningococcal vaccination _____ Type of vaccine received _____

Was the patient vaccination compliant with the ACIP guidelines or regional vaccination guidelines?

☐ Yes, provide version of ACIP guidelines that were in effect at the time of the event occurrence _____

☐ No, provide reason for non-compliance with ACIP or regional vaccination guidelines _____

If patient was not vaccinated against meningococcal infection prior to starting treatment with Amgen drug, provide the reason:

_____

Did the unvaccinated patient receive antibiotic prophylaxis when Amgen drug treatment was prescribed?

If yes: What type of antibiotic _____ Dose/Frequency _____ Route _____

Duration _____ Timing of the course of antibiotics in relation to Amgen drug treatment _____

If no prophylaxis antibiotics were prescribed, provide the reason:

_____

CONTINUED ON NEXT PAGE

AMGEN®

MENINGOCOCCAL INFECTION QUESTIONNAIRE

AER #

6. EVALUATIONS AND LABORATORIES AT TIME OF EVENT

Diagnostic	Results/Units	Normal Reference Range	Date	Report Attached Y	N
Blood pressure					
Respiratory rate					
Body temperature					
Heart rate					
O_2 saturation					
Hemoglobin					
Hematocrit					
WBC with differential					
Neutrophils					
Platelet count					
CRP					
Fibrinogen					
D-Dimer					
BUN/Creatine					
LDH					

Diagnostic	Results/Units	Normal Reference Range	Date	Report Attached Y	N
K+					
Na+					
Ca++					
Mg++					
Phosphorus					
Chloride					
Arterial blood gases					
Urinalysis					
Blood specimen:					
culture PCR positive gram stain					
CSF specimen:					
culture PCR positive gram stain					
Other specimens: (please specify)					
Neisseria meningitidis serotype identified:					

7. REPORT RESULTS (indicate date performed dd/mm/yyyy)

X-rays _____

MRI _____

CT _____

Biopsy/Pathology reports _____

Other (please specify) _____

Consultation reports _____

8. EVENT CLINICAL COURSE (indicate and provide dates dd/mm/yyyy)

What was the event final diagnosis? _____

Was the patient admitted to intensive care unit (ICU)? ☐ Yes ☐ No _____

☐ If yes, provide date of ICU admission _____

Any complications present? (Provide details): _____

☐ Organ system failure _____

☐ Mechanical ventilation _____

☐ Vasopressor treatment _____

Did the event resolve? ☐ Yes ☐ No Date of resolution _____

Did the patient die due to the event? ☐ Yes (date of death) _____ ☐ No

☐ Autopsy performed (provide summary results) _____

What treatment was provided for the event? (e.g., antibiotics, transfusions, skin grafts, etc.) please specify dose, frequency, route of administration

_____

_____

_____

_____

☐ Other treatment (e.g. hemodialysis): _____

_____

☐ Any sequelae due to event (specify) _____

_____

9. ADDITIONAL COMMENTS (please provide additional relevant details as necessary)

_____

_____

_____

REPORTER Name:
Address:
City:
Country:
State/ Province:
Email:
Postal Code:
Phone: (include country code)

Amgen
Office Fax:

CONTINUED FROM PREVIOUS PAGE

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable.

Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Draft key messages of the additional risk minimization measures

The marketing authorization holder (MAH) shall agree the details of educational material including a patient card with each National Competent Authority and must implement such programs nationally to ensure that:

1. All healthcare professionals who may prescribe eculizumab receive the appropriate educational material.
2. All patients being treated with BEKEMV receive a patient card.
3. Vaccination reminders are sent to the prescribers or pharmacists that intend to prescribe/dispense eculizumab.

The educational material should be agreed with the National Competent Authority and should contain the following:

- Summary of Product Characteristics
- Patient Information Leaflet
- Guide for healthcare professionals
- Guide for patients/parents/caregivers
- Patient card
- Vaccination reminders are sent to the prescribers or pharmacists that intend to prescribe/dispense BEKEMV

The educational materials for healthcare professionals shall include:

- Summary of Product Characteristics
- Guide for healthcare professionals

The guide for healthcare professionals to prescribing should contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection and sepsis, especially of *Neisseria meningitidis* and other *Neisseria species*, including disseminated gonorrhoeae.
- All patients must be monitored for signs of meningococcal infection.
- The need for patients to be vaccinated against *Neisseria meningitidis* 2 weeks prior to receiving eculizumab and/or to receive antibiotic prophylaxis. Patients must be vaccinated and revaccinated according to current national guidelines for vaccination use.
- Sorbitol content warning and the risks for patients with HFI when intravenously exposed to sorbitol.

- BEKEMV contraindication in patients with HFI (regardless of their age), and in children below 2 years of age, who may not yet be diagnosed with HFI.
- The need to explain to and ensure understanding of by patients/parents/carers:
  - the risks of treatment with eculizumab
  - the signs and symptoms of sepsis/severe infection and what action to take
  - the patients/parents/caregivers guides and their contents
  - the need to carry the patient card and to tell any healthcare professional that he/she is receiving treatment with eculizumab
  - the requirement for vaccinations/antibiotic prophylaxis and revaccination according to current national guidelines for vaccination use
  - the risks of serious metabolic harms due to treatment with BEKEMV if the patient also has HFI

The educational materials for patients/parents/caregivers shall include:

- Patient Information Leaflet
- Guide for patients/parents/caregivers
- Patient card

The guide for patients/parents/caregivers should contain the following key messages:

- Treatment with eculizumab increases the risk of severe infection, especially *Neisseria meningitidis* and other *Neisseria species*, including disseminated gonorrhoeae.
- Signs and symptoms of severe infection and the need to obtain urgent medical care.
- The patient card and the need to carry it on their person and tell any treating healthcare professional that they are being treated with eculizumab.
- The importance of meningococcal vaccination prior to treatment with eculizumab and/or to receive antibiotic prophylaxis.
- The patient must be vaccinated and revaccinated according to current national guidelines for vaccination use.
- The need for children to be vaccinated against pneumococcus and *Haemophilus influenzae* before eculizumab treatment.
- The risk of severe thrombotic microangiopathic 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.
- The risks of serious metabolic harms (potentially life-threatening) due to treatment with BEKEMV if the patient also has HFI.
- BEKEMV contraindication in patients with HFI (regardless of their age), and in babies and children below 2 years of age, who may not yet be diagnosed with HFI.

The patient card should contain:

- Signs and symptoms of infection and sepsis.
- Warning to seek immediate medical care if above are present.
- Statement that the patient is receiving eculizumab.
- Statement that the patient must receive vaccination and revaccination according to current national vaccination guidelines for vaccination use.
- The vaccination and revaccination dates should be included on the patient card.
- Sorbitol content warning and potentially life-threatening risks of patients with HFI who are intravenously exposed to sorbitol-containing medicines.
- BEKEMV contraindication in patients with HFI (regardless of their age), and in babies and children below 2 years of age, who may not yet be diagnosed with HFI.
- Contact details where a healthcare professional can receive further information.

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense BEKEMV, a reminder in order that the prescriber/pharmacist checks if a (re)-vaccination against *Neisseria meningitidis* is needed for his/her patients on BEKEMV.

Annex 7. Other Supporting Data (Including Referenced Material)

References

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Annex 8. Summary of Changes to the Risk Management Plan Over Time

Table 25. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
1.1	Date of RMP: 15 April 2024 Date of Approval: 07 May 2024 Procedure: EMEA/H/C/005652/IB/0004	**Safety Concerns** Important Identified Risks: The following important identified was added: • Severe TMA complications due to drug discontinuation in aHUS patients The following important potential risks were removed: • Malignancies and hematologic abnormalities in paroxysmal nocturnal hemoglobinuria patients • Serious infections in neonates after maternal exposure to eculizumab **Pharmacovigilance Plan** • Removed the following questionnaires: o Initial pregnancy questionnaire (mother) o 6 to 8 weeks post due date questionnaire (mother) o Six and twelve month infant questionnaire o Lactation questionnaire **Postauthorization Efficacy Plan** No change **Risk Minimization Measures** • Added routine risk minimization measures to minimize the risk of severe TMA complications due to drug discontinuation in aHUS patients • Revised the details of the additional risk minimization measure of physician's guide and patient's/parent's information brochure for the important identified risk of severe TMA complications due to drug discontinuation in aHUS patients • Removed routine and additional risk minimization measures for the important potential risks of malignancies and hematologic abnormalities in paroxysmal nocturnal hemoglobinuria patients and serious infections in neonates after maternal exposure to eculizumab **Annexes** • Removed the following questionnaires from Annex 4: o Initial pregnancy questionnaire (mother) o 6 to 8 weeks post due date questionnaire (mother) o Six and twelve month infant questionnaire o Lactation questionnaire • Language in the physician guide to prescribing and in the patient's/parent's information brochure in Annex 6 was updated to include aHUS.

Table 25. Summary of Changes to the Risk Management Plan Over Time

Version	Date of RMP Approval Date Procedure	Change
2.0	Date of RMP: 13 August 2025 Date of Approval: To be determined Procedure: To be determined	**Safety Concerns** The following risks were removed: • Important identified risk of *Aspergillus* infection • Important potential risks of Serious hemolysis after drug discontinuation in paroxysmal nocturnal hemoglobinuria patients and Immunogenicity **Pharmacovigilance Plan** No change **Postauthorization Efficacy Plan** No change **Risk Minimization Measures** Additional risk minimization measures revised **Annexes** • Annex 6: Details for the revised additional risk minimization measures updated