EU risk management plan for Aspaveli® (pegcetacoplan)

RMP version to be assessed as part of this application:

RMP version number:	3.0
Data lock point for this RMP:	13 November 2023
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Rationale for submitting an updated RMP: Revised regarding the PAS-studies

Summary of significant changes in this RMP: Revised regarding the PAS-studies Sobi.PEGCET-301 and Sobi.PEGCET-302. Epidemiology section Part II: Module SI has been updated. Exposure data has been updated per the DLP 13 November 2023.

Other RMP versions under evaluation: N/A

Details of the currently approved RMP:

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QPPV name: Martin Bowling

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the MAH's QPPV. The electronic signature is available on file.

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List of abbreviations

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ADA	Antidrug antibodies
AE	Adverse event
AH50	50 % alternative hemolytic complement pathway activity
APL-2	Pegcetacoplan
ARC	Absolute reticulocyte count
ATC	Anatomical therapeutic chemical
BMF	Bone marrow failure
BMTx	Bone marrow transplantation
CFB	Change from baseline
CH50	50 % classical hemolytic complement pathway activity
C_{max}	Maximum serum concentration
CNS	Central nervous system
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay
ERN RITA	European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases
ESID	European Society for Immunodeficiencies
EU	European Union
EVH	Extravascular hemolysis
FACIT	Functional Assessment of Chronic Illness Therapy
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FLAER	Fluorescent aerolysin
GPI	Glycosylphosphatidylinositol
Hb	Hemoglobin
HSC	Hematopoietic stem cells
IgA	Immunoglobulin A
IgM	Immunoglobulin M
INN	International nonproprietary name
IPIG	International PNH Interest Group
ISR	Injection site reaction
IVH	Intravascular hemolysis
LDH	Lactate dehydrogenase

Abbreviation	Definition
LLN	Lower limit of normal
LS	Least square
MAC	Membrane attack complex
MAH	Marketing authorization holder
MAVE	Major adverse vascular event
N/A	Not applicable
NAb	Neutralizing antibody
OLP	Open-label period
PASS	Post-authorization safety study
PEG	Polyethylene glycol
PEG40	Polyethylene glycol (40-kDa nominal molecular weight)
PIG-A	Phosphatidylinositol N acetylglucosaminyltransferase subunit A
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
PSUR	Periodic Safety Update Report
PT	Preferred term
Q	Quarter
QPPV	Qualified person for pharmacovigilance
RBC	Red blood cell
RCP	Randomized controlled period
RMP	Risk management plan
ROW	Rest of world
SAE	Serious adverse events
s.c.	Subcutaneous
SmPC	Summary of product characteristics
SMQ	Standardized medical dictionary for regulatory activities query
SOC	System organ class
TE	Thrombotic event
TEAE	Treatment-emergent adverse event
UK	United Kingdom
ULN	Upper limit of normal
US	United States

Part I: Product overview

Table 1 Product overview

Active substance(s) (INN or common name)	Pegcetacoplan
Pharmacotherapeutic group(s) (ATC Code)	L04AJ03
Marketing Authorization Holder	Swedish Orphan Biovitrum AB (publ)
Medicinal product(s) to which this RMP refers	1
Invented name(s) in the EEA	Aspaveli
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Pegcetacoplan is a symmetrical molecule composed of 2 identical pentadecapeptides covalently bound to the ends of a linear 40-kDa PEG molecule. The peptide moieties bind to complement C3 and exert a broad inhibition of the complement cascade. The 40-kDa PEG moiety imparts improved solubility and longer residence time in the body after administration of the drug product.
	Summary of mode of action: Pegcetacoplan binds to complement protein C3 and its activation fragment C3b with high affinity, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH, EVH is facilitated by C3b opsonization, and IVH is mediated by the downstream MAC. Pegcetacoplan exerts broad regulation of the complement cascade by acting proximal to both C3b and MAC formation, thereby controlling the mechanisms that lead to EVH and IVH. These functions of pegcetacoplan underly the observed sustained reduction in complement-mediated hemolytic activity in patients with PNH.
	Important information about its composition: The pegcetacoplan bulk drug substance is manufactured as a white to off-white, porous, solid lyophilized material of low bulk density. Pegcetacoplan is very soluble in water and acetate buffer pH 5.0 containing [redacted] sorbitol [redacted]. Pegcetacoplan solution for s.c. infusion 1080 mg/20 mL is a sterile, aqueous, acetate-buffered sorbitol solution. The drug product is filled in 20-mL, single-use, clear Type I glass vials.
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	Aspaveli is indicated as monotherapy in the treatment of adult patients with PNH who have hemolytic anemia.

Dosage in the EEA	Pegcetacoplan is administered as twice weekly s.c. doses of 1080 mg. For patients switching from a C5 inhibitor, for the first 4 weeks, pegcetacoplan is administered in addition to the patient's current dosage of C5 inhibitor treatment. After 4 weeks, the patient should discontinue C5 inhibitor and continue on monotherapy with pegcetacoplan. Switches from complement inhibitors other than eculizumab have not been studied. Discontinuing other complement inhibitors before reaching steady state of pegcetacoplan should be done with caution (see section 5.2).
Pharmaceutical form(s) and strength(s)	Solution for infusion, 1080 mg
Is/will the product be subject to additional monitoring in the EU?	Yes.

Abbreviations: ATC, Anatomical therapeutic chemical; EEA, European Economic Area; EU, European Union; EVH, Extravascular hemolysis; INN, International nonproprietary name; IVH, Intravascular hemolysis; MAC, Membrane attack complex; PEG, Polyethylene glycol; PNH, Paroxysmal nocturnal hemoglobinuria; RMP, Risk management plan; s.c., Subcutaneous.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Treatment of adult patients with paroxysmal nocturnal hemoglobinuria

Pegcetacoplan (APL-2) is a C3 inhibitor that has been developed for the treatment, via s.c. infusion, of adults with PNH. PNH is a rare, chronic, acquired, potentially life-threatening hematologic disease characterized by debilitating complement-mediated hemolytic anemia as well as BMF and an increased risk of thrombosis.

Incidence:

PNH is rare, and although it has been reported globally, the exact worldwide incidence and prevalence remain unknown. In Europe, the annual incidence of PNH has been reported as 1.3 to 2.98 per 1 000 000 (1, 2).

Prevalence:

Evidence of the prevalence of PNH in the EU is very limited and dependent on methods for identifying cases and the definition of PNH. With a conservative approach using a very wide definition of PNH, the prevalence is estimated to be around 0.4/10,000 persons (3) with diagnosed PNH likely to be substantially lower (4).

Demographics of the population in the proposed indication and risk factors for the disease:

PNH is an acquired, chronic genetic disorder that affects all populations and both sexes.

The demographic data is largely based on data from the International PNH Registry (5).

Median age at disease onset for PNH was 35.5 years (mean age 39.3 years), and men and women were equally represented (female 53 %) within the registry (5).

PNH is associated with aplastic anemia and other bone marrow disorders. Almost 63 % of the patients who had not yet initiated eculizumab had a history of BMF, and about 53 % had a history of aplastic or hypoplastic anemia. The proportion of patients with BMF was highest among the patients with the smaller clone size (89.2 % of patients with a clone >10 %) and lowest in those with the larger clone size (46.0 % of patients with a clone >50 %) (5). In addition to BMF, other bone marrow disorders, including myelodysplastic syndromes, myelofibrosis, and/or acute myeloid leukemia, have been reported before or after diagnosis with PNH (5-8).

The main existing treatment options:

Historically, management of PNH was limited to the use of supportive measures, such as blood transfusions and anticoagulation therapy. The risk of TEs in patients with PNH remained high. Anticoagulation therapy could reduce the risk of thrombosis, but complications, such as hemorrhage, are frequent (8, 9).

BMTx and complement inhibitor therapies are the only effective therapies for the treatment of PNH. The only potentially curative therapy for PNH is allogeneic BMTx; however, this procedure is associated with substantial morbidity and mortality (10-12). Although bone marrow function may be restored in up to half of patients receiving a transplant, considerable challenges and risks (e.g., graft failure and infection) reserve this option for patients with severe BMF, reoccurring life-threatening thromboembolic incidences, or refractory transfusion-dependent hemolytic anemia (13, 14).

Complement 5 (C5) inhibitors

In general, C5 inhibition is the current standard to treat PNH (15, 16). Eculizumab was authorized in the EU for use in adult patients with PNH in 2007 (17), and ravulizumab received market authorization in 2019 (18). Eculizumab and ravulizumab share a common mechanism of action in that they are humanized monoclonal antibodies that specifically bind 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. A key structural difference between eculizumab and ravulizumab is the substitution of 4 amino acids in the complementarity-determining and Fc regions of eculizumab, which causes an enhanced endosomal dissociation of C5 and recycling to the vascular compartment through the neonatal Fc receptor pathway. This gives ravulizumab a terminal half-life that is 4 times that of eculizumab (19).

C5 inhibition effectively reduces IVH as evidenced by the reduction of LDH (11, 19-21). Treatment with C5 inhibitors results in improved outcomes of disease in patients with PNH (19-22). Eculizumab reduces hemolysis (i.e., IVH as measured by LDH), fatigue, transfusion requirements, and improvements in quality of life (20, 22). It is also associated with a 92 % reduction in the risk of TE and improved patient survival (23, 24).

Because of the terminal inhibition of complement, in most patients treated with eculizumab, surviving PNH erythrocytes are destined for EVH by accumulating C3 fragments (opsonins) on the surface (25-28). Ongoing EVH leading to continued anemia in patients treated with eculizumab is common (8, 27-29). In retrospective real-world studies of eculizumab, 72 % of patients with PNH remain anemic, 36 % require 1 or more transfusions per year (27), and up to 89 % of patients demonstrate evidence of ongoing IVH as well as EVH (29). In addition, 13 % were treated with higher doses (1200 mg) or with shorter administration interval (10 to 12 days) because of ongoing hemolysis (29).

In a phase 3 clinical study of patients with PNH previously treated with eculizumab and randomized to either ravulizumab or eculizumab, LDH normalization was achieved by 64 of 97 patients (66.0 %) treated with ravulizumab and 58 of 98 patients (59.2 %) treated with eculizumab, and similar proportions of patients on ravulizumab and eculizumab achieved Hb stabilization (~76 %) (19). Taken together, a proportion of patients with PNH still have underlying hemolysis, which may lead to clinically significant sequalae (8, 28).

The most serious risk of C5 inhibitors is a 1000- to 2000-fold increase in the risk of neisserial infections that can be life-threatening. Therefore, vaccination against *Neisseria meningitidis* should be administered prior to starting treatment with complement inhibitors; however, patients treated with C5 inhibitors remain at risk for meningococcal disease even after receipt of meningococcal vaccines (30-32).

Supportive therapy

Despite treatment with complement inhibitors, supportive therapy may still be needed to manage ongoing symptoms or manifestations of PNH; however, none of these supportive measures modify the course of hemolytic PNH, and patients without access to complement inhibition ultimately die from their disease. Management of PNH with supportive measures include RBC transfusions to lessen ongoing hemolysis and reduce anemia (33). In addition, folate supplementation remains necessary to support increased erythropoiesis in the bone marrow during ongoing hemolysis (13). Anticoagulant therapy has been used prophylactically (34) and in the management of thrombosis (13); however, the risk of thromboembolism remains high (11, 35). For events of breakthrough hemolysis, corticosteroids can be used but have a potential long-term toxicity (12, 13). Prior to complement inhibition, iron supplements were used because of renal losses (hemoglobinuria, hemosiderinuria) (12).

Natural history of the indicated condition in the PNH population, including mortality and morbidity:

The natural history of patients with PNH is highly variable. The disease can arise de novo or evolve from acquired aplastic anemia. No universally accepted classification scheme is available, but the IPIG classifies PNH into 3 categories (adopted from a classification first used by de Latour et al.) (8, 35): classical PNH (in which patients have clinical manifestations of hemolysis or thrombosis), PNH in the context of other primary bone marrow disorders (such as aplastic anemia or myelodysplastic syndromes), and subclinical PNH (in which patients have low proportions of PNH clones but no clinical or laboratory evidence of hemolysis or thrombosis) (8, 24).

Patients with hemolytic PNH tend to have near-physiological platelet and neutrophil counts, LDH levels more than 2 times the upper physiological limit (indicative of IVH), a normocellular bone marrow, an increased reticulocyte count, and a relatively large (usually >50 %) population of PNH granulocytes. Patients with aplastic anemia PNH (acquired aplastic anemia with a low-to-moderate proportion of a PNH clone) are severely pancytopenic. They tend to have hypocellular bone marrow, relatively low ARCs, and low percentages of PNH granulocytes. Patients who had a PNH clone identified by flow cytometry but did not fulfill the criteria of either category were classified as intermediate PNH (8). The proportion of patients with a history of BMF was lower in patients who had higher percentages of GPI-deficient granulocytes at baseline (5). The median granulocyte clone size at enrollment (for C5 inhibitor-untreated patients) or at the start of treatment with C5 inhibitors in the PNH International Registry was 31.8 % (5).

In patients with PNH untreated by complement inhibitors, 61.3 % (2219 of 3620) had a history of RBC transfusions, 20.2 % had a history of anticoagulation therapy, and 38.8 % had a history of immunosuppressive therapy at baseline. History of anticoagulant use was correlated with increasing clone size, and history of immunosuppressive therapy was negatively correlated with the clone size (both significantly) (5). Patients had a high burden of disease at baseline. A majority of the patients (55.8 %) had hemolysis, defined by an LDH ratio ≥1.5 times the ULN at baseline and impaired renal function (42.8 % with estimated glomerular filtration rate <90 mL/min/1.73 m^2 and 15.0 % with estimated glomerular filtration rate <60 mL/min/1.73 m^2) (5) . There was a significant increase in the percentage of patients with LDH levels ≥1.5 × the ULN as PNH clone size increased: in patients with a clone size less than 10 %, 9.7 % of the patients had LDH levels ≥1.5 × the ULN; in patients with a clone size of 10 % to 49 %, 48.3 % had LDH levels ≥1.5 × the ULN; and in patients with a clone size of 50 % or more, 89 % had LDH levels ≥1.5 × the ULN (5).

A small proportion of patients have been observed to experience a spontaneous remission of their disease, usually many years after their initial diagnosis; however, for the majority of patients, PNH requires chronic management (9).

Morbidity, common symptoms, and AEs of PNH from large real-world PNH populations were studied in a UK-based cohort and in the International PNH Registry (5, 8, 9, 24).

Almost all patients who were enrolled in the International PNH Registry (93.3 %) reported at least 1 PNH-related symptom. 80 % reported fatigue, with 91.4 % reporting at least 1 additional symptom. Other commonly reported symptoms were dyspnea (64 %), headache (63 %), and hemoglobinuria (62 %); 38 % of men experienced erectile dysfunction (8).

Anemia in PNH is often multifactorial and can result from a combination of hemolysis and BMF. IVH with moderate-to-severe anemia, an increased ARC, a normal-to-increased mean corpuscular volume (the average volume of RBCs), and a markedly increased level of LDH are common in hemolytic PNH (8, 9, 24).

Disabling fatigue, a common feature of PNH, can be disproportionate to the degree of anemia. Fatigue is frequently most intense during a hemolytic attack but was commonly reported to be present at all times (8). Fatigue was reported by more than 80 % of the patients enrolled in the International PNH Registry (5).

Smooth muscle dystonia is also common. Abdominal pain (44 %), back pain, esophageal spasm, dyspnea (64 %), and erectile dysfunction (38 % of male patients) are common manifestations associated with hemolytic PNH and are often a direct consequence of IVH and the release of free Hb. Smooth muscle dystonias are more common in patients with large proportions of PNH granulocyte clones and patients with markedly increased levels of LDH (7, 8).

Episodes of jaundice and hemoglobinuria were reported by almost 50 % of patients. These signs and symptoms can be constant or paroxysmal and are often exacerbated by infections, surgery, exercise, pregnancy, or excessive alcohol intake. Hemoglobinuria (passing urine of a color ranging from dark tea to black to cherry red, owing to high levels of Hb in the urine) was reported by 62 % of patients with PNH (depending on the cohort or study) (8).

Patients with PNH have an increased risk of chronic kidney disease as a result of long-term IVH. Renal tubular damage can occur from microvascular thrombosis, accumulation of iron deposits, or both (8). 43 % of patients had a history of impaired renal function at enrollment in the registry (5).

Other commonly reported symptoms included headache (63 %), scleral icterus (~45 %), chest pain (33.5 %), and confusion (~30 %). Although each of the common PNH-related symptoms were reported in all categories of clone size, patients with clone sizes 50 % or over reported significantly more hemoglobinuria, dyspnea, abdominal pain, scleral icterus, erectile dysfunction, and dysphagia. Mild-to-moderate pulmonary hypertension has also been reported (5, 7, 8) . Among PNH patients untreated with a C5 inhibitor, with the exception of fatigue, the proportions of patients with each symptom were significantly correlated with increasing GPI-deficient granulocyte clone size category, although a large proportion of patients with clone size <50 % experienced each symptom (5).

In the 6 months prior to completion of the baseline questionnaire, 194 of 856 patients (22.7 %) reported being hospitalized because of their PNH. Patients were significantly more likely to be hospitalized if they had a history of thrombosis or had experienced self-reported PNH-related symptoms of scleral icterus, chest pain, dysphagia, abdominal pain, hemoglobinuria, dyspnea, or fatigue in the past 6 months (7).

Thrombosis is the most common cause of mortality in PNH (accounting for almost 50 % of deaths before complement inhibition therapy was introduced). Venous thrombosis tends to be more common than arterial thrombosis. Hepatic vein thrombosis (Budd-Chiari syndrome) is the most common occurrence; other sites frequently affected by thrombosis include abdominal (e.g., portal, mesenteric, and splenic) and cerebral (sagittal and cavernous sinus) veins. Deep vein thrombosis, pulmonary emboli, and dermal thrombosis are also relatively common. PNH-associated TEs occur in up to 30 % of patients in Western countries but only <15 % of patients in Asian countries. Of the patients enrolled into the International PNH Registry, 18.8 % had a history of MAVEs when enrolled or starting C5 inhibitor treatment, and 13.3 % specifically experienced TEs. The proportions of patients with a history of MAVEs or TEs at baseline correlated significantly with a larger clone size. Thrombosis might occur in aplastic anemia PNH but is less common than in hemolytic PNH (5, 8, 9, 24).

During follow-up of patients in the International PNH Registry, outcomes included TEs (2 %), of which 26.1 % were arterial or venous TE. Overall, 37.7 % needed RBC transfusion during follow-up. Before C5 inhibitors were available, the percentage of patients who suffered 1 or more episodes of venous TE was much higher (39 %), and it was often fatal or life-threatening. Hospitalization for PNH complications was reported for 23 % of patients, and 17 % attributed lack of ability to work to PNH (7-9, 24).

Morbidity and mortality in PNH have improved substantially over the past 30 years because of increased awareness, monitoring of disease, and improved treatment options for patients with PNH. Analyses of smaller and larger cohorts of patients with PNH show that life expectancy following diagnosis was about 10 and 20 years in the 1990s and 2000s, respectively (8, 9, 22, 23, 35). Mortality is mostly attributed to events of thrombosis; additional causes include hemorrhage and infection (9, 22, 23, 26, 35). In historical control of patients from a retrospective study who were treated with supportive care before the introduction of eculizumab, 20 % died within

6 years of diagnosis (23). In patients who were enrolled into the International PNH Registry, more than 15.5 % had a history of TEs at baseline. Although thrombosis might occur in patients with both aplastic anemia and PNH, it is less common than in patients with classic PNH (7-9, 24). With the introduction of the complement inhibitor eculizumab, life expectancy has increased with the reduction in the risk of TEs (22, 23).

For the 122 patients who have died since enrollment into the International PNH Registry, the highest risk of death (11.7 %) was in patients who met the diagnostic criteria for PNH and aplastic anemia (24).

Important comorbidities:

BMF is an associated disorder. BMF can occur independently of PIG-A mutations in patients with PNH and can contribute to the clonal expansion of PIG-A mutant HSCs. BMF in PNH might be caused by autoimmunity to HSCs, a mechanism similar to that observed in idiopathic aplastic anemia (8). In a cohort of patients with PNH who referred to Hammersmith Hospital in London between 1940 and 1970 (80 patients), 29 % of patients received a diagnosis of aplastic anemia before the diagnosis of PNH. At the time of the PNH diagnosis, 80 % had thrombocytopenia, and 55 % had neutropenia (9).

Almost 63 % of the C5 inhibitor-naive patients in the International PNH Registry had a history of BMF, and about 53 % (2206/4201) had a history of aplastic or hypoplastic anemia at baseline. The proportions of patients with BMF showed an inverse correlation with clone size (5). Many patients in the registry have aplastic anemia as their primary diagnosis because the registry allows inclusion of patients with ≥0.01 % PNH clone (8). Overall, 774 (48.1 %) of patients in the registry had been diagnosed with 1 or more types of bone marrow disease, including aplastic anemia or hypoplastic anemia (n=701; 43.5 %), myelodysplastic syndromes (n=93; 5.8 %), myelofibrosis (n=7; 0.4 %), and/or acute myeloid leukemia (n=6; 0.4 %) (7). Concomitant immunosuppressive therapy is administered if necessary (8). Of patients with aplastic anemia, 38.5 % were on immunosuppressive therapy when they enrolled in the International PNH Registry, 21 % were on anticoagulation therapy, and 5 % were on both (7).

Part II: Module SII - Nonclinical part of the safety specification

Key safety findings from nonclinical studies and relevance to human usage:

Key safety findings from nonclinical studies	Relevance to human usage
Toxicity	
• Pegcetacoplan evoked microscopic nonadverse epithelial vacuolation and infiltrates of vacuolated macrophages in multiple tissues in both species (rabbits and monkeys). • Observed with similar incidence and severity in PEG40-treated animals. • These findings were neither accompanied by abnormal clinical signs nor evidence of cellular distortion, necrosis, degeneration, inflammation, or disturbed body function. • No-effect dose not determined in rabbits, and 1 mg/kg/d in monkeys in chronic toxicity studies.	These findings are attributed to the PEG40 moiety of pegcetacoplan and have been reported with numerous other PEGylated peptide/protein pharmaceuticals, including marketed ones. They are widely considered to represent an adaptive tissue response to long-chain PEG and are regarded as nonadverse.
• Pegcetacoplan was associated with microscopic renal tubular degeneration in rabbits and monkeys. • Spatial association with vacuolation suggests that the degeneration may represent a response to locally extreme tissue concentrations of PEG. • Renal degenerative changes were considered adverse, although they did not rise to a level considered to be dose limiting. • Degeneration was minimal and nonprogressive between 1 month and 9 months of dosing and was not accompanied by increases in serum urea nitrogen or creatinine (markers of overt renal dysfunction) in either species. • No-effect dose not determined in rabbits, and 7 mg/kg/d in monkeys in chronic toxicity studies.	Significance to humans of the minimal renal degeneration observed in the animal studies is not known. The no-adverse-effect level for this finding in monkeys (the pharmacologically relevant species) was 7 mg/kg/d, with C_{max} exposure 1.45× that of the intended human clinical dose. No signal to suggest disturbed renal function has been detected in the current cumulative clinical safety database for pegcetacoplan. Overall, data from a phase 1 study to evaluate the effect of renal impairment had no effect on the PK of pegcetacoplan; therefore, no dose adjustment is required for patients with renal impairment.
Safety pharmacology	
• Pegcetacoplan does not inhibit the human ether-à-go-go gene-encoded ion channel. • Single s.c. doses up to 140 mg/kg in monkeys did not affect cardiac or respiratory function. • Pegcetacoplan effects on the CNS were not investigated because pegcetacoplan does not cross the blood-brain barrier. No abnormal CNS-related clinical signs were observed in repeat-dose toxicity studies.	Pegcetacoplan poses no significant risk for negative cardiopulmonary effects. Pegcetacoplan does not cross the blood-brain barrier, and the potential for negative CNS effects is low.

Key safety findings from nonclinical studies	Relevance to human usage
• Pegcetacoplan had no effect on embryofetal development (rats, rabbits, or monkeys). • In an enhanced prenatal/postnatal development study in monkeys, pegcetacoplan at the high dosage (28 mg/kg/day) was associated with an increase in abortions and stillbirths. This was not a predicted pharmacological effect of pegcetacoplan. • Placental transfer and excretion into milk were demonstrated but were minimal (<1 %) and not pharmacologically relevant. • No-effect dose for increased incidence of abortions and stillbirths 7 mg/kg/d in monkeys.	The clinical relevance of the increase in abortions and stillbirths observed in the monkeys is not known. The no-adverse-effect level for this finding in monkeys (the pharmacologically relevant species) was 7 mg/kg/d, with C_{max} exposure 1.34× that of the intended human clinical dose. The current weight of evidence suggests that complement cascade regulation is beneficial to pregnancy maintenance, and targeted complement therapeutics are used to control adverse pregnancy outcomes. Pregnant and breastfeeding women were excluded from clinical trials.
Other toxicity-related information	
• Pegcetacoplan is not genotoxic (neither mutagenic nor clastogenic) and was not teratogenic in animal studies. • Pegcetacoplan was weakly to moderately antigenic in rabbits but minimally antigenic in monkeys. • Rodent carcinogenicity studies of pegcetacoplan have not been conducted.	Pegcetacoplan is not a genotoxic hazard. There is no evidence from toxicity studies that pegcetacoplan is an endocrine disrupter, a cell-cycle dysregulator, or a proinflammatory agent. The current weight of evidence suggests complement activation enhances tumor growth and metastasis, and complement inhibition has been postulated as a potential oncology therapy.

Abbreviations: C_{max}, Maximum serum concentration, CNS, Central nervous system; PEG, Polyethylene glycol; PEG40, Polyethylene glycol (40-kDa nominal molecular weight); PK, Pharmacokinetics; s.c., Subcutaneous.

Part II: Module SIII - Clinical trial exposure

The clinical development program for pegcetacoplan in PNH included 6 clinical pharmacology studies as well as the following 7 studies (5 completed and 2 ongoing) in adult and pediatric subjects with PNH:

- APL2-CP0514 (Pharoah): This is a completed phase 1b open-label, prospective, nonrandomized, single and multiple ascending dose study in 12 subjects (9 unique subjects). The objective was to assess the safety, tolerability, and PK of single and multiple s.c. doses of pegcetacoplan in subjects with PNH who were still anemic during treatment with eculizumab.
- APL2-202 (Palomino): This is a completed phase 2a, open-label, multidose study in 4 subjects. The objective was to assess the safety, tolerability, efficacy, and PK of multiple s.c. doses of pegcetacoplan in subjects with PNH who had not received treatment with eculizumab in the past.
- APL2-CP-PNH-204 (Paddock): This is a completed phase 1b, open-label, multiple ascending dose study in 23 subjects (22 unique subjects). The objective was to assess the safety, tolerability, preliminary efficacy, and PK of multiple s.c. doses of pegcetacoplan in subjects with PNH who had not received treatment with eculizumab in the past.
- APL2-302 (Pegasus): This is a completed global, phase 3, prospective, randomized, multicenter, open-label, active-comparator-controlled study in 80 subjects. The objective was to confirm treatment efficacy and safety of pegcetacoplan monotherapy for the treatment of PNH in subjects aged ≥18 years who were receiving eculizumab therapy but continued to have Hb levels <10.5 g/dL.
- APL2-308 (Prince): This is a completed phase 3, randomized, open-label study in 53 subjects. The objective was to evaluate the efficacy and safety of pegcetacoplan in subjects with PNH who were naive to treatment with any complement inhibitor within 3 months prior to screening.
- APL2-307: This is an ongoing open-label extension study for subjects who have completed a previous PNH pegcetacoplan study. The objective of the study is to establish the long-term safety and efficacy of pegcetacoplan in the treatment of PNH.
- APL2-PNH-209: This is an ongoing open-label, single-arm, phase 2 study to evaluate the safety, PK, and biologic activity of pegcetacoplan in pediatric patients with PNH. The primary objectives of this study are to define the PK of pegcetacoplan in adolescents with PNH; evaluate the efficacy of pegcetacoplan based on Hb level, LDH level, and ARC; and assess the safety of pegcetacoplan as measured by the incidence and severity of TEAEs, including bacterial infections.

Through 13 November 2023, 511 subjects have been exposed to systemic pegcetacoplan for 818.36 person-years; this includes 372 subjects exposed for >6 months and 279 subjects exposed for >1 year.

Table 2 Subject pegcetacoplan exposure in completed and ongoing PNH and other systemic-use studies as of 13 November 2023

Overall exposure									
Category/study	**Number of subjects with ≥1 pegcetacoplan dose**	**Duration of exposure category**							**Cumulative years on pegcetacoplan**
		>3 months	**>6 months**	**>1 year**	**>2 years**	**>3 years**	**>4 years**	**>5 years**	
All s.c. studies cumulative	**511**	**434**	**372**	**279**	**148**	**114**	**44**	**16**	**818.36**
Exposure by study for completed and ongoing PNH studies (s.c.)									
APL2-302	80	77	75	66	57	37	15	0	212.74
APL2-202	4	4	4	4	4	4	4	1	19.84
APL2-CP-PNH-204	22	18	18	18	14	14	14	14	80.39
APL2-CP0514	9	6	6	4	4	4	3	1	20.33
APL2-308	52	51	50	49	48	38	1	0	161.87
APL2-PNH-209	6	5	5	3	1	0	0	0	6.48
Cumulative	**173**	**161**	**158**	**144**	**128**	**97**	**37**	**16**	**501.65**
Exposure for other ongoing systemic-use studies (s.c.) [a]									
Cumulative	**338**	**273**	**214**	**135**	**20**	**17**	**7**	**0**	**316.71**

Abbreviations: IgA, Immunoglobulin A; PNH, Paroxysmal nocturnal hemoglobinuria; s.c., Subcutaneous.

a Exposure for other ongoing systemic-use studies represents the cumulative exposure of ongoing studies evaluating pegcetacoplan in warm antibody autoimmune hemolytic anemia cold agglutinin disease, IgA nephropathy, lupus nephritis, primary membranous nephropathy, C3 glomerulopathy, immune-complex membranoproliferative glomerulonephritis, and transplant-associated thrombotic microangiopathy after hematopoietic stem cell transplantation. For ongoing studies that were blinded as of the 13 November 2023 data cut-off date, the estimation was based on the randomization of subjects to receive either pegcetacoplan or placebo as per the specified randomization ratio (e.g., 2:1, 1:1, etc.) in the specific study protocols.

Note: Exposure in the long-term safety study, Study APL2-307, is included in the parent study. There were 6 patients who were treated with standard of care during Study APL2-308 and switched to pegcetacoplan when transitioning into Study APL2-307. Although only 46 subjects were treated with pegcetacoplan in Study APL2-308, these 6 subjects are counted in this table under this study.

The following tables present duration of exposure for the 5 completed PNH studies.

Table 3 Duration of exposure—pegcetacoplan number of subjects exposed and person-years of exposure as of 13 November 2023, by duration of exposure (completed PNH studies only, systemic exposure)

Cumulative for all indications (person-time)		
Duration of exposure	**Number of subjects with at least 1 pegcetacoplan dose**	**Person-years**
>3 months	149	129.08
>6 months	134	123.09
>1 year	47	57.60
>2 years	2	4.12
Any duration	161	130.43

Abbreviations: PNH, Paroxysmal nocturnal hemoglobinuria.
Note: Cumulative years on pegcetacoplan was calculated as duration in days between the first and last pegcetacoplan doses divided by 365.25, with long gaps in dosing subtracted for Study APL2-CP0514, Study APL2-CP-PNH-204, and Study APL2-302. The 5 completed PNH studies included in this table are Study APL2-CP0514, Study APL2-202, Study APL2-CP-PNH-204, Study APL2-302 and Study APL2-308.

Table 4 Age group and sex—pegcetacoplan number of subjects exposed and person-years of exposure as of 13 November 2023, by duration of exposure (completed PNH studies only, systemic exposure)

	Number of subjects with at least 1 pegcetacoplan dose	**Person-years**
Age group		
Adults (18 to 64 years)	137	112.17
Elderly (≥65 years)	24	18.26
Total	**161**	**130.43**
Sex		
Female	92	77.21
Male	69	53.22
Total	**161**	**130.43**

Abbreviations: PNH, Paroxysmal nocturnal hemoglobinuria.
Note: Cumulative years on pegcetacoplan was calculated as duration in days between the first and last pegcetacoplan doses divided by 365.25, with long gaps in dosing subtracted for Study APL2-CP0514, Study APL2-CP-PNH-204, and Study APL2-302. The 5 completed PNH studies included in this table are Study APL2-CP0514, Study APL2-202, Study APL2-CP-PNH-204, Study APL2-302 and Study APL2-308.

Table 5 Dose—pegcetacoplan number of subjects exposed and person-years of exposure as of 13 November 2023, by duration of exposure (completed PNH studies only, systemic exposure)

Planned dosing regimen	Number of subjects with at least 1 pegcetacoplan dose	Person-years
5 mg daily	2	0.25
30 mg daily	2	1.07
180 mg daily	3	2.15
270 mg daily	24	25.68
360 mg daily	4	6.60
1080 mg twice weekly	126	94.67
Total	**161**	**130.43**

Abbreviations: PNH, Paroxysmal nocturnal hemoglobinuria.
Note: Cumulative years on pegcetacoplan was calculated as duration in days between the first and last pegcetacoplan doses divided by 365.25, with long gaps in dosing subtracted for Study APL2-CP0514, Study APL2-CP-PNH-204, and Study APL2-302. The 5 completed PNH studies included in this table are Study APL2-CP0514, Study APL2-202, Study APL2-CP-PNH-204, Study APL2-302 and Study APL2-308.

Table 6 Ethnic origin—pegcetacoplan number of subjects exposed and person-years of exposure as of 13 November 2023, by duration of exposure (completed PNH studies only, systemic exposure)

Race	Number of subjects with at least 1 pegcetacoplan dose	Person-years
Asian	59	43.25
Black or African American	5	6.37
Native Hawaiian or other Pacific Islander	1	0.08
White	64	52.50
American Indian or Alaska Native	11	10.42
Other	5	4.22
Missing[a]	16	13.58
Total	**161**	**130.43**

Abbreviations: PNH, Paroxysmal nocturnal hemoglobinuria.
[a] Subjects with missing race are from sites in [redacted] where race was not collected because of privacy laws.
Note: Cumulative years on pegcetacoplan was calculated as duration in days between the first and last pegcetacoplan doses divided by 365.25, with long gaps in dosing subtracted for Study APL2-CP0514, Study APL2-CP-PNH-204, and Study APL2-302. The 5 completed PNH studies included in this table are Study APL2-CP0514, Study APL2-202, Study APL2-CP-PNH-204, Study APL2-302 and Study APL2-308.

Part II: Module SIV - Populations not studied in clinical trials

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

Patients excluded from pivotal clinical studies

1. **History of bone marrow transplantation**

Reason for exclusion: Allogeneic BMTx is the only potentially curative treatment for adults with PNH, although it carries the attendant risks of immunosuppression and graft-versus-host disease. It is only indicated in patients with PNH-associated BMF. BMTx would have obfuscated the interpretation of clinical data from Study APL2-302.

Is it considered to be included as missing information? No.

Rationale: BMTx is a rarely used intervention for PNH, and if the graft were successful in replacing the hematopoietic PNH clones, patients would not be candidates for further disease-modifying therapy. It is much more likely that pegcetacoplan would be used prior to BMTx or to delay it, and therefore BMTx would not cause a drug safety risk.

2. **Low platelet and neutrophil counts at screening (≤50 000/mm^3 and ≤500/mm^3, respectively)**

Reason for exclusion: These patients were excluded because low platelet and neutrophil counts can be indicative of BMF. Exclusion of these patients prevents confounding efficacy outcomes because of the low production of hematopoietic cells.

Is it considered to be included as missing information? Yes.

3. **Pregnant women**

Reason for exclusion: These patients are almost invariably excluded from clinical trials to manage the investigational drug safety risk. However, the sponsor believes there is a compelling interest to facilitate childbearing in patients with PNH, while preventing IVH and EVH in the safest way possible, and to provide prescriber and patient information. See Section SVII.1.2 for additional information.

Is it considered to be included as missing information? Yes

4. **Children**

Reason for exclusion: These patients are almost invariably excluded from clinical trials to manage the investigational drug safety risk. Sobi has an agreed pediatric investigational plan, including an ongoing open-label, single-arm, multicenter global study in adolescent subjects aged 12 to 17 years (Study APL2-PNH-209) which began in the Q3 of 2020.

Is it considered to be included as missing information? No.

Rationale: Pediatric patients are not part of the proposed target population.

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 7 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Study APL2-CP-PV-205 (a phase 1, single-dose, open-label study to evaluate the effect of renal impairment on the PK of APL-2) included 16 subjects. Study APL2-308 enrolled 53 subjects with PNH. This study permitted the inclusion of subjects with renal impairment. Of the 53 subjects enrolled, 35 were randomized to receive pegcetacoplan and 18 to receive standard of care (excluding complement inhibitors). 11 of the 18 subjects escaped to receive pegcetacoplan during the 26 week study. This study included previously untreated subjects with any Hb level less than the LLN at the screening visit (unlike Study APL2-302, which required subjects to have Hb level <10.5 g/dL at the screening visit).
Population with relevant different ethnic origin (included)	Japanese subjects: Study APL2-102 (a phase 1 single ascending dose study) included 20 subjects. Study APL2-302 included 12 Asian subjects.
Subpopulations carrying relevant genetic polymorphisms	N/A
Elderly patients (included)	24 subjects aged ≥65 years have been included in completed clinical studies of PNH.
Pediatric patients	Study APL2-PNH-209 (an open-label, single-arm, phase 2 study to evaluate the safety, PK, and biologic activity of pegcetacoplan in pediatric patients with PNH). 12 subjects (aged 12-17 years) planned. 3 subjects treated with pegcetacoplan.

Abbreviations: Hb, Hemoglobin; LLN, Lower limit of normal; N/A, Not applicable; PK, Pharmacokinetics; PNH, Paroxysmal nocturnal hemoglobinuria.

Part II: Module SV - Post authorization experience

SV.1 Postauthorization exposure

SV.1.1 Method used to calculate exposure

Since the distribution of pegcetacoplan is controlled, it is possible to get actual patient numbers exposed post marketing. The estimated patient-years can also be calculated from the number of dispensed vials and assuming 2 vials/week per patient (i.e., 1 vial every 3.5 days or daily dose 0.286 vial/day). Therefore, the estimated patient-years equals (number of dispensed vials × 3.5)/365.25.

SV.1.2 Exposure

The numbers of patients exposed and patient-years of exposure post marketing in the different global territories are presented below.

Table 8 Estimated cumulative patient exposure (as of 13 November 2023)

Region	Patients exposed	Patient-years exposed
EEA[a]	194	149.65
ROW[b]	393	476.93
Total	**587**	**626.58**

Abbreviations: EEA, European Economic Area; [redacted]

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

During the clinical development program there were no deaths or SAEs attributable to drug abuse or withdrawal, no overdoses, and no evidence of drug diversion or inappropriate self-administration. There is unlikely to be a potential for misuse with pegcetacoplan because it does not affect the CNS.

Evidence gathered to date does not suggest that pegcetacoplan has any risk of misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

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

Summary of safety concerns	
Important identified risks	None
Important potential risks	1. Serious infections 2. Serious hypersensitivity reactions 3. IVH after drug discontinuation 4. Immunogenicity 5. Malignancies and hematologic abnormalities 6. Potential long-term effects of PEG accumulation

Abbreviations: IVH; Intravascular hemolysis; PEG, Polyethylene glycol.

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

ISRs were reported in 37 % of subjects treated with pegcetacoplan during the RCP in the phase 3 pivotal clinical study, Study APL2-302. There were no ISR TEAEs that were serious or severe or led to study drug discontinuation.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

ISRs – There were 15 (of 41) subjects treated with pegcetacoplan during the RCP in Study APL2-302 who reported ISR TEAEs. Only 1 ISR was considered of moderate severity, and the rest were mild. There were no TEAEs of ISR that were serious or severe or led to study drug discontinuation.

The difference observed in drug-related TEAEs between the treatment groups in this study of s.c. administration is largely accounted for by ISRs, which were reported solely in the pegcetacoplan group. This was expected because subjects entering the study were already known to tolerate eculizumab by infusion administered every other week, and any preexisting AE related to eculizumab would be captured as medical history rather than a treatment-emergent AE.

Drug-related ISRs were also commonly reported in Study APL2-202, Study APL2-CP-PNH-204, and Study APL2-CP0514, which included daily dosing. ISRs occurred in 2 subjects (50.0 %) in Study APL2-202, 8 subjects (40.0 %) in Study APL2-CP-PNH-204, and 5 of 6 subjects in Study APL2-CP0514. As with Study APL2-302, no ISRs were severe or led to discontinuation in these studies.

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

Important identified risks:

None.

Important potential risk 1:

Serious infections

Increase in the incidence of infections and, specifically, meningococcal infections with the use of the marketed C5 inhibitor eculizumab (Soliris, Alexion Pharmaceuticals) has been established (30, 36-38). Eculizumab treatment is associated with a 1000- to 2000-fold increased incidence of meningococcal disease (32). In patients with PNH treated with eculizumab, the reported rate of meningococcal infection was 0.24 per 100 patient-years (38). The overall risk of serious infection (including all organisms) was 5.8 per 100 patient-years in patients with PNH and 7.9 in all patients (regardless of disease) treated with eculizumab (38). The FDA-approved prescribing information for eculizumab includes a boxed warning regarding the increased risk for meningococcal disease in eculizumab recipients. Increased rate of meningococcal infection increases the risk of sepsis and other adverse outcomes from these bacteria (39).

During Study APL2-302 RCP, the incidence of serious infections was relatively low. Overall, infections were reported by 12 subjects (29.3 %) and 10 subjects (25.6 %) in the pegcetacoplan and eculizumab groups, respectively, and the majority of events occurred in 2 or fewer subjects.

The majority of events in the pegcetacoplan group were mild (9 subjects [22.0 %]) or moderate (2 subjects [4.9 %]). 1 subject (2.4 %) experienced a severe SAE of gastroenteritis that was considered by the investigator to be unrelated to pegcetacoplan. The majority of events in the eculizumab group were mild (5 subjects [12.8 %]) or moderate (5 subjects [12.8 %]), and no subject experienced a severe event.

No events of meningitis have been reported.

1 subject (1.3 %) in the pegcetacoplan + eculizumab group experienced an SAE (sepsis) that was considered by the investigator to be possibly related to pegcetacoplan and eculizumab. Treatment with the study drug was not changed because of this event, and the event resolved after a week. 2 subjects (4.9 %) in the pegcetacoplan group experienced SAEs (mild bacterial infection and severe gastroenteritis). Both events were assessed as unrelated to pegcetacoplan, and subjects recovered without discontinuation of the study drug. No SAEs in the SOC of Infections and Infestations were reported in the eculizumab group.

Except for 1 event in each of the pegcetacoplan and eculizumab treatment groups, all reported events in the SOC of Infections and Infestations were considered by the investigator to be unrelated to the study drug. 1 subject (2.4 %) in the pegcetacoplan experienced viral upper respiratory tract infection considered by the investigator to be related to the study drug, and 1 subject (2.6 %) in the eculizumab group experienced sinusitis considered by the investigator to be related to the study drug.

There have been no reports of infections due to encapsulated bacteria or meningococcal infections through 161.7 person-years of systemic pegcetacoplan exposure. Of the 9 SAEs of sepsis and 1 SAE of biliary sepsis reported through 31 May 2020, 2 events that occurred in Study APL2-302 were deemed by the investigator to be treatment-related. The 2 subjects recovered and continued pegcetacoplan treatment. The microbiology investigations in these subjects did not identify pathogens. The subjects' prior medical history (i.e., renal transplant and immunosuppressant therapy and PNH-associated biliary disease) confounds the assessment of these 2 reports.

Risk-benefit impact:

It is unknown whether pegcetacoplan will follow the established increased risk of meningococcal infections or all serious infections in general identified for C5 inhibitors. Pharmacology data from Study APL2-302 shows that pegcetacoplan monotherapy down regulates the overall hemolytic activity of the complement system from both the classical and alternative pathways to a lesser extent than eculizumab monotherapy does.

- Mean CH50 at Week 16 in the pegcetacoplan group was 118.2 U/mL (CFB 110.5 U/mL), which was within the CH50 reference range (58 to 138 U/mL); mean CH50 was 16.4 U/mL (CFB 5.7 U/mL) in the eculizumab group.
- Mean AH50 (reference range of 76 to 176 U/mL) in the pegcetacoplan group was 66.2 U/mL (CFB 29.4 U/mL) and 45.3 U/mL (CFB 9.3 U/mL) in the eculizumab group.

Therefore, pegcetacoplan provides its clinical benefit for these PNH subjects while preserving a higher residual activity of both the classical and alternative pathways of complement, an important component in the protection against serious infections and specifically against infection caused by encapsulated bacteria.

Important potential risk 2:

Serious hypersensitivity reactions

The risk of serious hypersensitivity reactions is a theoretical risk that is based on the potential of any medicinal product and, specifically, a product structure including a PEG molecule.

There have been no reports of serious hypersensitivity reactions to date. There have been 2 reports of hypersensitivity. 1 was hypersensitivity of moderate severity in Study APL2-CP-PNH-204 deemed by the investigator to be related to pegcetacoplan. The event, which occurred on Day 1 (i.e., the subject's 1st day of dosing), led to the subject's discontinuation from the study. The subject tested negative for anti pegcetacoplan peptide antibody response before dosing on Day 1. The subject recovered with treatment and study drug discontinuation. 1 subject in Study APL2-CP-PNH-204 had a mild TEAE of maculopapular rash deemed by the investigator to be related to pegcetacoplan. This event was temporally associated with positive serum anti-PEG antibodies but not anti pegcetacoplan peptide antibodies. The rash was subsequently resolved, and anti-PEG serology became negative despite uninterrupted treatment with pegcetacoplan.

PEG is used to improve PK properties of medications, but concerns have been expressed about the immunogenicity of the PEG moiety itself (40). There are conflicting reports on the immunogenicity risk of PEG; although some do not consider the evidence for an anti-PEG antibody reaction convincing, others caution about loss of efficacy and increase of AEs because of anti-PEG antibodies, even if admitting that the information is very limited (40, 41).

All completed and ongoing clinical studies have evaluated the immunogenicity potential of pegcetacoplan using validated assays for assessment of anti pegcetacoplan peptide antibody and anti-PEG antibody in human serum samples. To date, no apparent correlation of antibody development to an altered PK profile has been observed. There has been no observed correlation of ADA development to clinical response or AEs in healthy or PNH subjects.

In the case of a serious hypersensitivity reaction, pegcetacoplan infusion should be immediately discontinued, and appropriate treatment needs to be instituted.

Risk-benefit impact:

Serious hypersensitivity reactions are an important potential risk; however, there have been no serious cases reported. There have been 2 reports of mild and moderate hypersensitivity reactions that were potentially related to pegcetacoplan. The subjects in these 2 cases recovered, and the events were resolved. Therefore, the available safety data from the PNH patient studies do not make serious hypersensitivity reactions an identified risk at the present time.

Important potential risk 3:

IVH after drug discontinuation

Uncontrolled complement activation leads to IVH mediated by the MAC and EVH mediated by accumulation of C3 fragments on RBC surfaces.

EVH is believed to be mediated by C3b opsonization rather than C5-dependent MAC-mediated IVH. C5 inhibition does not prevent C3b deposition on PNH RBCs; instead, it increases C3d deposition on PNH RBCs, thereby increasing EVH (25, 28).

Pegcetacoplan binds to human C3 and C3b, resulting in proximal inhibition of the complement cascade and control of both IVH and EVH. This mechanism of action protects the PNH RBCs from both types of hemolysis (42).

This broad protection allows PNH RBCs to accumulate rather than being constantly destroyed, leading to an increase in the percentage of Type II and Type III PNH RBCs in the blood of PNH patients. Discontinuation of treatment risks acute hemolytic crisis because of the high proportion of RBCs that will become vulnerable to destruction once again in patients with PNH (28).

No formal studies of withdrawal and rebound have been performed up to the data cut-off date (31 May 2020). However, abrupt discontinuation of pegcetacoplan treatment may result in the rapid lysis of the circulating PNH RBCs, unprotected against complement activation, potentially leading to severe anemia. A similar phenomenon is observed with discontinuation of C5 inhibitors, although the effect might be less severe because C5 inhibitors offer less complement protection, thus not allowing accumulation of as many PNH RBCs.

Hemolysis occurring in study subjects after sudden pegcetacoplan withdrawal has been observed. In Study APL2-204, 1 subject had pegcetacoplan administration withheld by the investigational site for 8 days, without consultation with the Sponsor, because of a herpes zoster infection. The subject was instructed by the investigator to resume administration immediately and received pegcetacoplan on the next 2 days. On the following day, the subject withheld pegcetacoplan dosing because of abdominal discomfort and was subsequently diagnosed with severe hemolysis. The gap in this subject's pegcetacoplan dosing was associated with the onset of hemolysis.

In Study APL2-CP0514, pegcetacoplan treatment was temporarily ceased for 1 subject following an SAE of alanine aminotransferase increased. 20 days later, the subject had an SAE of anemia that was attributed to rebound hemolysis following cessation of pegcetacoplan treatment.

Risk-benefit impact:

Hemolysis due to discontinuation of pegcetacoplan is an important potential risk. Furthermore, it is preventable, as detailed in the risk minimization measures in Part V. Therefore, the available safety data from the PNH patient studies do not make hemolysis due to discontinuation an identified risk at the present time.

Important potential risk 4:

Immunogenicity

Infrequent and generally transient anti pegcetacoplan peptide antibody responses have been detected in pegcetacoplan-treated subjects across all clinical studies. Based on currently available data, no discernible impact of anti pegcetacoplan peptide antibody has been identified on the PK/PD, efficacy, or safety profile of pegcetacoplan.

Risk-benefit impact:

Immunogenicity is an important potential risk based on the known potential of all medicinal products and the class effect of all therapeutic proteins. No risk factors have been identified for the risk of immunogenicity in patients with PNH, neither within the conducted clinical trials for PNH nor identified in published literature.

Important potential risk 5:

Malignancies and hematologic abnormalities

Malignancies

The complement system plays a role in immune editing of malignancies. It can play an active protumorigenic role in tumor progression. Chronic inflammation promoted by complement proves to be protumorigenic at different levels—promoting cell death and compensatory proliferation; inducing Tregs, which impair cancer immunity; and promoting immunesuppressive myeloid environment (myeloid-derived suppressor cells, neutrophils, etc). However, the complement system may also promote acute inflammation and participate in mechanisms of immune surveillance directly targeting tumor cells at the early stages of tumor development. It may also be a key player in promoting complement-dependent cytotoxicity-mediated killing of cancer cells (43).

Scientific literature is replete with examples of increased complement activation and tissue deposition in human cancers (lung, ovarian, cervical, melanoma, glioblastoma, etc) being correlates of prognosis. Preclinical studies have shown the efficacy of combinatorial approaches of using a checkpoint inhibitor along with a complement inhibitor, which have a synergistic effect on reducing tumor burden (44). Although more studies are needed to determine the effect of eculizumab or pegcetacoplan on cancer remission in the backdrop of PNH, there is at least 1 case report that shows a prolonged remission of cancer in a patient following eculizumab therapy for PNH (45).

Long-term animal studies have not been performed to test pegcetacoplan for its carcinogenic potential. The genotoxic potential of pegcetacoplan and PEG40 was assessed in a standard Good Laboratory Practice-compliant battery of genetic toxicity assays, including in vitro bacterial reverse mutation (Ames), in vitro micronucleus (TK6 cells), and an in vivo micronucleus assay in mice. The uniformly negative results of the genotoxicity assays indicate that pegcetacoplan is not mutagenic or clastogenic.

During Study APL2-302 RCP, 1 subject (1.3 %) experienced a moderate TEAE of basal cell carcinoma on Day 113 that was considered to be unrelated to pegcetacoplan by the investigator. The event was ongoing at the end of the RCP but resolved on Study Day 185 of the open-label phase. Pegcetacoplan dosing was not changed because of this event.

Risk-benefit impact:

The benefits of C3 inhibition far outweigh the risk despite the dual role of complement in cancer. The evidence of the tumor surveillance role of complement far outweighs the evidence of its tumor-promoting role. Additional clinical data available from Study APL2-302 with pegcetacoplan treatment up to 16 weeks supports this conclusion. Reported events were consistent with what is expected in patients with PNH. The majority of these events were nonserious in nature and were not considered related to pegcetacoplan.

Hematologic abnormalities

PNH is an acquired, clonal, nonmalignant hematologic disease characterized by complement-mediated RBC hemolysis with or without hemoglobinuria, an increased susceptibility to thrombotic episodes, and/or some degree of bone marrow dysfunction (8). PNH is caused by complement-mediated lysis of erythrocyte clones lacking functional CD55 and CD59 on their surface to protect them against this process. As such, these erythrocytes are particularly susceptible to the formation of the MAC and have been shown to lyse readily in the presence of complement activation (8).

During the RCP, 7 subjects (17.1 %) in the pegcetacoplan group experienced an event in the SOC of Blood and Lymphatic Disorders. 2 subjects (4.9 %) experienced mild events, 2 subjects (4.9 %) experienced moderate events, and 3 subjects (7.3 %) experienced severe events. 2 subjects (4.9 %) experienced severe hemolysis, and 1 subject (2.4 %) experienced thrombocytopenia. 2 subjects (4.9 %) experienced SAEs of hemolysis that were considered to be unrelated to pegcetacoplan by the investigator. 2 subjects (4.9 %) experienced TEAEs of hemolysis considered to be related to pegcetacoplan by the investigator.

Risk-benefit impact:

Hematologic abnormalities is an important potential risk for pegcetacoplan. Pegcetacoplan has proven to be superior to C5 inhibitors in improving Hb levels, transfusion avoidance, ARC, and breakthrough hemolysis. There is no definitive evidence that pegcetacoplan use is associated with increase in the risk of hematologic abnormalities. Benefits of treatment with pegcetacoplan outweigh the potential increased risk of developing hematologic abnormalities.

Important potential risk 6:

Potential long-term effects of PEG accumulation

Based on the current available nonclinical and clinical data for pegcetacoplan, a possible impact of potential accumulation of PEG in tissues on clinical safety after long-term treatment cannot be excluded with reasonable certainty.

In nonclinical studies with pegcetacoplan, there were no adverse findings related to the CNS or liver, and the observed renal findings occurred at higher doses of PEG than the intended clinical dose. The clinical relevance of these findings is unknown, and patients will be monitored for any risk related to accumulation of PEG in the ongoing long-term extension study and in the proposed PASS (Sobi.PEGCET-301).

Risk-benefit impact:

Potential long-term effects of PEG accumulation are an important potential risk for pegcetacoplan. Available safety data derived in clinical trials with pegcetacoplan, although limited regarding the number of patients and treatment duration, did not reveal any signals hinting at adverse effects of PEG accumulation.

Missing information 1:

Use in patients with BMF

Patients with low platelet (≤50 000/mm^3) or neutrophil count (≤500/mm^3) at screening were excluded from PNH clinical trials to avoid competing risks for complications and avoid premature study treatment discontinuation unrelated to PNH.

A study from 2016 on the 122 patients who have died since enrollment in the International PNH Registry (21.1 % of patients in the aplastic anemia PNH category were treated with eculizumab during their follow-up in this study) reported the highest risk of death (11.7 %) in patients who met the diagnostic criteria for PNH and aplastic anemia (the classification rule for PNH with aplastic anemia included low platelet and neutrophil counts, but at different thresholds than the pegcetacoplan development program) compared with other categories (24).

Risk-benefit impact:

It is unknown whether the risk profile of PNH patients with BMF due to treatment with pegcetacoplan will be different. Information on the risk in PNH patients with BMF will be collected in the post marketing stage (see Part III).

Missing information 2:

Use in pregnant women

There are insufficient data on pegcetacoplan use in pregnant women to suggest a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes up to the data cut-off date (31 May 2020).

Animal reproduction studies with pegcetacoplan were conducted in rats, rabbits, and cynomolgus monkeys. Pegcetacoplan treatment of pregnant cynomolgus monkeys at a s.c. dosage of 28 mg/kg/day (2.9 × the human steady-state C_{max}) from the gestation period through parturition resulted in a statistically significant increase in abortions or stillbirths compared with controls. This was not a predicted pharmacological effect of pegcetacoplan. No maternal toxicity or teratogenic effects were observed in offspring delivered at term. Additionally, no developmental effects were observed in infants up to 6 months' postpartum. Systemic exposure to pegcetacoplan was detected in fetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the 2nd trimester, but the exposure was minimal (<1 %, not pharmacologically significant).

Historically, pregnancy has been discouraged in patients with PNH. The management of PNH during pregnancy has been challenging because pregnant patients can have more severe IVH, and morbidity and mortality are higher among pregnant patients with PNH than among those with PNH who are not pregnant; these risks continued to be high during the postpartum period (46). However, outcomes in pregnant women with PNH who were treated with complement C5 inhibitors were comparable with those in the general population in terms of the live birth rate and maternal complication rate (38). Most patients who progressed past the 1st trimester had their C5 inhibitor dosage increased because of breakthrough of terminal complex blockade and consequent hemolysis (8). It is conceivable that facilitating prevention of both IVH and EVH would be beneficial in pregnant patients with PNH. One (1) pregnancy was reported during the pegcetacoplan development program in a female subject in Cohort 4 of Study APL2CP0514. Administration of pegcetacoplan to this subject was immediately stopped following laboratory confirmation of the pregnancy. At the time pegcetacoplan was discontinued, the subject was approximately 5 weeks' pregnant. Antenatal ultrasound scans were normal, and the subject delivered a full-term baby with no complications reported during delivery. No abnormalities were reported in the infant's health.

Pregnant women are almost invariably excluded from clinical trials to manage the investigational drug safety risk and were excluded from the clinical development program. Prescriber and patient information will be provided and pharmacovigilance activities (see Part III) have been added.

Risk-benefit impact:

It is unknown whether the risk profile of women during pregnancy will be different with respect to treatment with pegcetacoplan. After authorization, the safety of pegcetacoplan in pregnancy will be monitored using routine pharmacovigilance.

Missing information 3:

Long-term safety (>1 year)

As of 31 May 2020, 187 subjects have been exposed to systemic pegcetacoplan for 161.7 person years (including PNH and non-PNH indications).

Risk-benefit impact:

PNH is a rare, chronic, acquired genetic disorder that can have debilitating and disabling symptoms. Therefore, it is expected that patients will require long-term or perhaps life-long treatment for their disease.

Although side effects following chronic treatment with pegcetacoplan are unknown, based on the current clinical experience, additional safety concerns with long-term treatment are not anticipated. Given the severity of PNH and the limitations and risks associated with the use of the current available therapies, the impact of lack of longer-term safety data on the risk-benefit balance, although unknown, is not expected to significantly affect the known safety profile of pegcetacoplan. After authorization, in addition to routine pharmacovigilance, the long-term safety of pegcetacoplan will be evaluated in Sobi.PEGCET-301 PASS (see Part III).

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

No safety concerns have been added in this version of the RMP.

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

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

Important identified risk:

None.

Important potential risk:

Serious infections

Potential mechanisms:

The complement system is a crucial part of the innate immune system. It comprises over 30 membrane-bound and soluble components and has 3 major functions: (1) host defense by opsonization, chemotaxis, induction of inflammation, and lysis of targets; (2) interfacing between innate and adaptive immunity by augmenting the antibody response and immunological memory; and (3) the disposal of waste through the clearance of apoptotic cells and immune complexes (36).

The complement system protects against bacteria through separate and complementary mechanisms. The 2 main mechanisms are opsonization by anchoring C4b and C3b to a bacterial membrane that promotes phagocytosis and the formation of the MAC, which induces lysis of gram-negative bacteria through membrane pore formation (47). Bacterial labeling with C3-derived products also enhances antigen presentation to B cells and thereby triggers the development of an adaptive immune response.

Gram-negative bacteria are the main concern because they are the target of the MAC. Upon contact with bacterial cells, complement precursors are activated to act as the body's first line of defense through a variety of responses. The most rapid response is the formation of ring-structured pores, the MAC or C5b-9, that directly kills gram-negative bacteria within minutes. Gram-positive bacteria are resistant to the MAC, probably because their thick peptidoglycan outer layer prevents insertion of the MAC into the cell membrane (37).

The main effector functions of complement are driven by the cleavage of 2 central complement proteins: C3 and C5. The complement cascade is triggered by the recognition of bacteria via soluble pattern-recognition molecules or antibodies that bind both gram-positive and gram-negative bacteria (separated on the basis of different cell wall composition). All recognition pathways converge in the formation of convertase enzymes on the surface of the bacterium. First, C3 convertases cleave complement protein C3 to generate C3b that exposes a reactive thioester bond; this can covalently attach to hydroxyl groups of carbohydrates on the bacterial surface. When C3b molecules are covalently deposited onto the bacterial surface, these efficiently trigger and facilitate phagocytosis by immune cells. C3b (and its breakdown product, iC3b) are recognized by complement receptors on myeloid (CR1, CR3, and CR4) and Kupffer cells (CRIg) and enhance the engulfment of opsonized particles, leading to intracellular (microbial) killing. The labeling of bacterial cells with C3 derived activation products also stimulates an adaptive immune response by directing the transport of bacteria to lymphoid organs and by enhancing antigen presentation to adaptive immune cells (37).

Another role of the deposited C3b molecules is to alter the specificity of the C3 convertase. At high local C3b densities, C3 convertases change into C5 convertases, meaning that they switch substrate from C3 to C5. Activation of C5 results in the release of peptide C5a, a strong chemoattractant that helps recruit phagocytes toward the site of infection and induces an oxidative burst. Additionally, C5a-mediated stimulation of basophils and mast cells triggers the production of histamine and subsequent vasodilatation (37).

Complement-dependent bacterial killing is one of the most rapid ways to kill an invading bacterium. Although both the labeling of bacteria with C3b and the MAC-dependent killing of gram-negatives occur within minutes, phagocyte attraction and subsequent intracellular killing takes longer (estimated as 30 minutes to 1 hour). The fact that pathogenic bacteria have evolved mechanisms to resist various steps in the complement cascade strongly supports the crucial role of complement in human defense against bacteria (37).

The ESID and ERN RITA Complement Guideline from 2020 summarizes primary immunodeficiencies and their consequences. Increased susceptibility to infection caused by encapsulated organisms is a key clinical consequence of inherited defects in the complement system (36). Specifically, deficiency of C3 and its regulators (factor H and factor I) has been associated with severe recurrent bacterial infections (48). Primary C3 deficiency is rare, with only about 20 cases reported in the literature. Because of its central position in the complement cascade and the variety of functions it serves, which include neutrophil chemotaxis, opsonophagocytosis, and serum bactericidal activity, these individuals suffer severe, recurrent infections caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *N. meningitidis* (48). Properdin and terminal component deficiencies result in an increased risk of neisserial infections (36); classical pathway deficiencies are often related to encapsulated bacteria such as *S. pneumoniae* (47).

The alternative pathway is a highly conserved surveillance system that is continuously turning over (undergoing tick-over) because of a labile thioester bond in C3 and thus does not require antibodies or lectins for activation. Properdin is a positive regulator of alternative pathway activity and works by stabilizing alternative pathway convertases. Properdin deficiency is a rare, hereditary, primary immunodeficiency (total number of known cases globally >100). Patients are unusually susceptible to neisserial infections. The deficiency manifests with either complete absence of the molecule (Type I), partial deficiency (Type II), or a normal level of dysfunctional protein (Type III). Properdin-deficient individuals are susceptible to meningococcal disease, which is frequently complicated by sepsis and most commonly occurs in adolescence (36). However, the presence of even small quantities of C3 tends to lessen the risk of infection in terms of frequency and severity (49).

Evidence source(s) and strength of evidence:

Increase in the incidence of infections and, specifically, meningococcal infections with the use of eculizumab has been established (30, 38). The rate of serious infection with eculizumab (a marketed C5 inhibitor) treatment in patients with PNH was 5.8 per 100 patient-years. Between 2007 and 2016, the rate of meningococcal infection in patients treated with eculizumab varied from 0.16 to 0.63 per 100 patient-years (38). 8 deaths (15.4 % of cases) occurred in PNH patients treated with marketed C5 inhibitors with meningococcal infections, mostly because of delays in diagnosis and/or treatment of infection (38).

Inhibition of components of the complement system, including C3, might decrease innate immunity to encapsulated bacteria. This potentially increases the risk of serious infections from these bacteria in patients treated with pegcetacoplan. Studies have identified increased susceptibility to infection caused by encapsulated organisms as a key clinical consequence of congenital complement deficiency. Specifically, deficiency of C3 and its regulators (factor H and factor I) has been associated with severe recurrent bacterial infections caused by *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* (48).

There have been no reports of meningococcal infections through 818.36 person-years of systemic pegcetacoplan exposure in ongoing and completed clinical trials and 626.58 person-years of systemic pegcetacoplan exposure in the post-marketing setting.

Characterization of the risk:

There is no clear evidence so far that pegcetacoplan increases the risk of serious infections. Prior experience of PNH patients treated with C5 inhibitors and review of published data describing the risk of infection in patients with congenital complement deficiencies is the main reason for including serious infection as an important potential risk.

There were no events of sepsis reported in the RCP in Study APL2-302; however, 3 subjects experienced 3 severe SAEs in the OLP coded as postprocedural sepsis, biliary sepsis, and sepsis. The cases of postprocedural sepsis and sepsis (1 subject [1.3 %] each) were deemed by the investigator to be unrelated to pegcetacoplan. The case of biliary sepsis (1 subject [1.3 %]) was deemed by the investigator to be related to pegcetacoplan. Treatment dose in this subject was increased because of biliary sepsis. The 1 subject (1.3 %) who experienced sepsis withdrew from treatment due to the event. All 3 subjects recovered.

In Study APL2-308, there were no events of sepsis reported in the RCP; however, in the post-RCP, 1 subject (2.2 %) in the pegcetacoplan group and 1 subject (5.6 %) in the standard of care group experienced a severe serious TEAE of septic shock. Both events were fatal; however, neither event was deemed related to pegcetacoplan.

There have been no reports of meningococcal infections through the data cut-off date (13 November 2023).

In Study APL2-302, at the end of 48 weeks, the types of events reported were generally consistent with those previously observed with pegcetacoplan treatment, and the incidence of infections was consistent with what was expected, given that the OLP was longer than the RCP. In Study APL2-308, there was no greater risk of infection seen in the pegcetacoplan group (8 subjects [17.4 %]) than the standard of care group (5 subjects [27.8 %]). Across all PNH studies (APL2-302, APL2-202, APL2-PNH-209, APL2-CP-PNH-204, ALP2-CP0514, APL2-307, and APL2-308), the majority of AEs were not serious or severe, and there were no unexpected events and no AEs of meningitis.

The incidence rates for meningococcal infections are 7000- to 10 000-fold higher in patients with late complement component deficiency than in the general population (49) and 1000- to 2000-fold higher in patients receiving a marketed C5 inhibitor, eculizumab, under risk mitigation measures than in the general population (30). It should be noted that those with inherited complement deficiency are at risk from birth, whereas those treated with eculizumab are not at risk before they start complement inhibitor therapy. These findings suggest that the current mitigation measures are generally effective. Although approximately 95 % of patients with meningococcal infections were reported to have received vaccinations, patients were not vaccinated against all serotypes (38).

The risks of bacterial infections and sepsis in patients treated with eculizumab were reported on the basis of long-term post marketing safety monitoring in broader populations (38). Safety data were collected from spontaneous and solicited sources from 16 March 2007 through 01 October 2016. Cumulative exposure to eculizumab in patients with PNH was 21 016 patient-years. The incidence rate of any serious infections in patients treated with eculizumab was 5.8 per 100 patient-years for all infections; among all serious infections, sepsis was 11.7 % (38).

52 patients with cases of meningococcal infection in patients with PNH were reported, resulting in a case rate of 0.24 per 100 patient-years. Of the 52 patients, 29 were female (55.8 %), and 23 were male (44.2 %); the majority of cases occurred in patients aged 16 to 44 years (41 patients), and 23 patients (44.2 %) were aged 16 to 25 years. 8 of the 52 meningococcal infection cases resulted in mortality (0.03 per 100 patient-years). The median time to onset of meningococcal infection after the 1st dose of eculizumab was 272 days (range was 4 to 2247, excluding 18 patients who did not have enough information to calculate the time) (38).

The rate of meningococcal infections reported for patients treated with eculizumab for PNH or atypical hemolytic uremic syndrome tended to decrease over time, ranging from 0.57 per 100 patient-years in 2007 to 0.16 per 100 patient-years in 2016. Almost all cases occurred in patients with previous confirmed meningococcal vaccination, with no obvious geographical predilection noted, and serogroup B remained the most frequently reported meningococcal infection despite introduction of the serogroup B meningococcal vaccine in 2013. The mortality rate associated with meningococcal infections remained stable over time, with no deaths observed between 2012 and 2016 (38).

Although these estimates are based on long-term follow-up of a large PNH population, several factors limited their accuracy and consistency. Some of the cases were reported spontaneously, but some were solicited. The rate of infections and specifically of *N. meningitidis* infection changed over time with vaccine availability and varied across subgroups of patients and by comorbidities. The case definitions that were used, and specifically the case definition of sepsis, was not consistent over time and across reports (38).

A review published in 2013 by Hillmen and colleagues (50) included reporting on the safety of treatment with the same marketed C5 inhibitor, eculizumab, based on data from the clinical development program. The 36-month safety profile of treatment was based on 195 patients with hemolytic PNH who participated in 1 of 3 prospective parent trials: a phase 2 pilot study and its extensions, a double-blind, placebo-controlled phase 3 study and a phase 3 open-label study (50). At the end of these initial studies, 187 of the 195 patients (95.9 %) enrolled in an open-label extension study. All patients had a minimum of 10 % PNH RBCs at enrollment in the parent trials and were vaccinated with a meningococcal vaccine at least 14 days before the 1st eculizumab infusion in the parent studies. All 3 parent trials employed the same dosing regimen: 600-mg infusions of eculizumab every week for 4 weeks followed 1 week later by a single 900-mg dose and then a maintenance dose of 900 mg every 14 days until the end of the study. In the extension study, patients continued to receive the maintenance dose of eculizumab (50).

Safety assessments included solicited monitoring of AEs, clinical laboratory tests, and vital signs. All AEs were reviewed for events that could potentially be related to an infection. 40 patients (20.5 %) reported a total of 67 serious infection-related TEAEs, none of which were fatal. 2 cases of meningococcal sepsis were reported during treatment, an infection rate of 0.42 per 100 patient-years. Neither of the patients with meningococcal sepsis had received vaccination against the specific strain of their infection. At the time of the infections, serum bactericidal antibody values were within an appropriate range and both infections resolved with treatment and without sequelae. 1 was a serotype B infection that occurred in a [redacted] patient 353 days after the initiation of eculizumab. This patient had received a quadrivalent vaccine against serotypes A, C, W135, and Y. The infection was successfully treated with several antibiotics, and the patient continued treatment with eculizumab. The other case occurred in a [redacted] patient 416 days after eculizumab treatment was initiated and was due to serotype Y or W135 (further serotyping was not possible in this patient's country). This patient had been vaccinated against serotypes A and C. This infection was successfully treated with multiple antibiotics, but the patient discontinued treatment (50).

Additional reported cases of infection, besides the 2 patients with meningococcal sepsis (1 %; mean 385 days onset from start of treatment) included 2 patients with sepsis (1 %; mean 604 days onset from start of treatment), 2 with septic shock (1 %; mean 312 days onset from start of treatment), and 1 case of staphylococcal infection, which was successfully treated with antibiotics, although the patient withdrew from the study (50).

Additional evidence on the risk of meningococcal disease in eculizumab-treated patients can be found in a review of existing meningococcal disease case investigation records (30). 16 cases of meningococcal disease were identified in eculizumab recipients in the US for the period 2008 to 2016. The majority of cases (11) were caused by nongroupable *N. meningitidis* and occurred in patients who had documentation of receipt of at least 1 dose of meningococcal vaccine before disease onset.

Risk factors and risk groups:

Although C3 inhibition has the potential to impact an individual's ability to mount an adaptive immune response, therapeutic complement inhibition during adulthood is less likely to be detrimental than congenital C3 deficiency because adaptive immunity in older individuals has already been established and developed. Most of these effects can be managed with appropriate prophylactic measures, such as immunization and antibiotic therapy. C3 inhibition by pegcetacoplan may not result in broad adverse infection associated with C3 deficiency because the manifestations of primary complement deficiencies may not be adequate indicators of the safety of complement therapeutics.

In addition, alternative immune mechanisms to address infections in the absence of MAC deficiency associated with C3 inhibition are likely to exist, particularly in the inflammatory milieu of PNH. For example, although targeting C3 is likely to increase the risk of infections by encapsulated bacteria, such as *N. meningitidis*, because of downstream MAC deficiencies associated with C3 inhibition, activated phagocytes in the absence of the MAC have been shown to contribute to the killing of *N. meningitidis*, albeit with less efficiency. This is often mediated by activated neutrophils and other immune cells (51).

Risk groups:

- Unvaccinated patients or patients who do not maintain sufficient antibodies to the vaccines given before or during treatment might have a higher risk of infection due to encapsulated bacteria.
- Patients with PNH-associated BMF (including aplastic anemia PNH and myelodysplastic syndrome) have a higher risk of serious infection due to neutropenia (24, 33, 38).
- For patients who had solid organ (renal) transplant or BMTx, receiving immunosuppressive treatment (e.g., high-dose steroids, mycophenolate mofetil, ciclosporin, and tacrolimus) is a risk factor (38).
- Individuals exposed to certain bacteria through work or travel might have a higher risk of infection. Groups at risk may include day-care workers, laboratory workers, military personnel, and other individuals with heightened levels of exposure to pathogenic bacteria.

Preventability:

Vaccinations against encapsulated organisms, including *S. pneumoniae, N. meningitidis*, and *H. influenzae* can help mitigate the risk of infection. 2 weeks prior to initiating treatment with pegcetacoplan, patients are required to be vaccinated against *S. pneumoniae; N. meningitidis* A, C, W, Y, and B; and *H. influenzae*. No vaccines are contraindicated in patients with complement deficiencies, meaning that live vaccines can be administered. The efficacy of vaccines in patients with complement deficiencies has not been evaluated in large studies (36). However, there is evidence that in a complement deficiency population, vaccine does not confer full protection (47).

In addition to vaccination, prophylactic antibiotic therapy can be administered at the discretion of the treating physician in accordance with local treatment guidelines for patients with PNH who are receiving treatment with a complement inhibitor. Broad-spectrum antibiotic coverage should be provided to patients who are not yet vaccinated and, where appropriate, the vaccine should be given time to work.

Vaccination boosters are required periodically as recommended by the ACIP for patients with complement deficiencies as determined by the healthcare professional or as required by Member States (52).

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection according to the updated consensus definition by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine (53). For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential (Sepsis-related) Organ Failure Assessment score of 2 points or more (53).

Sepsis cannot be predicted; thus, early identification is critical. Patients with suspected infection who are likely to have a prolonged stay in an intensive care unit or to die in the hospital can be promptly identified at the bedside with a quick Sequential Organ Failure Assessment clinical score (criteria are alteration in mental status, systolic blood pressure of 100 mmHg or less, or respiratory rate ≥22/minute) (53).

To minimize the risk, patients should be monitored for early signs of meningococcal infections and other serious infections and evaluated immediately if infection is suspected. To that end, mitigation measures, including vaccinations, safety cards, and educational materials for patients and physicians will be implemented (see Part V).

Impact on the risk-benefit balance of the product:

In Study APL2-302, pegcetacoplan monotherapy provided sustained improvements in Hb across the entire study (mean CFB of 2.69 g/dL at Week 48 for all subjects on pegcetacoplan monotherapy). In Study APL2-308, pegcetacoplan demonstrated superiority with regard to Hb stabilization. The majority of subjects in the pegcetacoplan group (85.7 %) and no subjects in the standard of care group achieved Hb stabilization through Week 26 (P<0.0001). Pegcetacoplan demonstrated superiority with regard to Hb response. The majority of subjects in the pegcetacoplan group (71.4 %) and 1 subject in the standard of care group (5.6 %) achieved an increase of ≥1 g/dL in Hb concentration (P<0.0001).

In Study APL2-302, over 70 % of subjects were transfusion-free at Week 48 (73.2 % of subjects who continued on pegcetacoplan during the OLP and 71.8 % of subjects who switched to pegcetacoplan during the OLP). In Study APL2-308, pegcetacoplan demonstrated superiority with regard to the proportion of subjects who received a transfusion or had a decrease in Hb concentration of >2 g/dL. The majority of subjects (91.4 %) in the pegcetacoplan group and 5.6 % of subjects in the standard of care group had transfusion avoidance (P<0.0001).

In Study APL2-302, ARC, a marker of hematopoietic bone marrow compensatory activity in the setting of anemia, was improved and sustained with pegcetacoplan monotherapy across the entire study (CFB -132.05 × 10^9/L at Week 48). In Study APL2-308, pegcetacoplan demonstrated superiority with regard to CFB in ARC at Week 26, with LS mean changes of -123.26 × 10^9 cells/L in the pegcetacoplan group and -19.44 × 10^9 cells/L in the standard of care group (P=0.0002).

In Study APL2-302, LDH level (a marker of IVH) was decreased from baseline on pegcetacoplan therapy, and control was maintained across the entire study; 56.1 % of subjects achieved LDH normalization in the absence of transfusion at Week 48. In Study APL2-308, pegcetacoplan demonstrated superiority with regard to CFB in LDH at Week 26, with LS mean changes of -1870.5 U/L in the pegcetacoplan group and -400.09 U/L in the standard of care group (P<0.0001).

In Study APL2-302, pegcetacoplan monotherapy demonstrated clinically meaningful improvement in FACIT-Fatigue Scale score across the entire study, and a 10.12-point increase in FACIT-Fatigue Scale score was seen on pegcetacoplan monotherapy at Week 48. In Study APL2-308, the proportion of subjects achieving improvement of ≥3 points in FACIT-Fatigue Scale score, which is generally considered clinically meaningful, was greater in the pegcetacoplan group (60 %) than in the standard of care group (11.1 %) at Week 26.

The safety data in Study APL2-302 support the conclusion that the overall safety of pegcetacoplan is similar to that of eculizumab through Week 16. Continuation of pegcetacoplan monotherapy through Week 48 demonstrated a favorable safety profile. No unexpected safety concerns associated with the use of pegcetacoplan in patients with PNH were observed. In

Study APL2-308, pegcetacoplan was well tolerated, and the safety findings in this study were consistent with the known safety profile of pegcetacoplan.

The benefits of pegcetacoplan, therefore, outweigh the risks.

The risk will be further characterized in the Sobi.PEGCET-301 PASS (see Part III: Pharmacovigilance plan, Section III.2). This will allow better quantification of the risk in a real-world population.

Public health impact:

The safety profile of pegcetacoplan is similar to that of marketed C5 inhibitors, according to experience in the clinical development program to date.

In Study APL2-302, at the end of 48 weeks, the types of events reported were generally consistent with those previously observed with pegcetacoplan treatment, and the incidence of infections was consistent with what was expected, given that the OLP was longer than the RCP. In Study APL2-308, there was no greater risk of infection seen in the pegcetacoplan group than the standard of care group. Across all PNH studies (APL2-302, APL2-202, APL2-PNH-209, APL2-204, APL2-307, APL2-308 and APL-CP0514), the majority of AEs were not serious or severe, and there were no unexpected events and no AEs of meningitis.

The incidence of death related to serious infection, including meningitis, is expected to be no higher than that of the marketed C5 inhibitors.

If these incidences are reflected after marketing, then a positive risk-benefit ratio will be maintained.

There have been no reports of meningococcal infections in 818.36 person-years of systemic pegcetacoplan exposure in ongoing and completed clinical trials. It is expected that the risk will be noninferior to marketed C5 inhibitors and, therefore, no increase in cases after marketing is expected.

In the post marketing setting, there have been no reports of serious infection due to encapsulated bacteria attributable to pegcetacoplan in 626.58 person-years of systemic pegcetacoplan exposure.

Important potential risk 2:

Serious hypersensitivity reactions

Potential mechanisms:

The risk of serious hypersensitivity reactions is a theoretical risk that is based on the potential of any medicinal product and, specifically, a product structure including a PEG molecule. Drug hypersensitivity reactions are unpredictable adverse drug reactions. They manifest either within 1 to 6 hours following drug intake (immediate reactions) with mild to life-threatening symptoms of serious hypersensitivity reactions or several hours to days later (delayed reactions), primarily as exanthematous eruptions (54).

Pegcetacoplan, the active ingredient in pegcetacoplan solution for s.c. infusion 1080 mg/20 mL, is a symmetrical molecule composed of 2 pentadecapeptides covalently bound to the ends of a linear 40-kDa PEG molecule. The peptide moieties bind to complement C3 and exert a broad

inhibition of the complement cascade. The 40-kDa PEG moiety imparts improved solubility and longer residence time in the body after administration of the drug product.

PEG has very low toxicity and, because of its simple structure, is assumed to be of low immunogenicity (40).

Recently, several reports correlated the generation of anti-PEG antibodies with loss of therapeutic efficacy, and there has been an increase of reported adverse effects after repeated administrations (41). However, there are conflicting reported results on both the level of anti-PEG antibodies found and the level of correlation (if any) with efficacy and AEs (40).

A study reported a high occurrence (22 % to 25 %) of anti-PEG IgM antibodies in normal donors. These IgM antibodies were also identified with a hemagglutination assay using PEG-coated erythrocytes. This higher incidence of anti-PEG antibodies in the normal population compared with the incidence found in an earlier study is often cited in the literature as evidence of an increasing incidence of preexisting anti-PEG antibodies, which may compromise the use of PEGylated biopharmaceuticals and other PEGylated forms of therapy. However, although comparable assay technologies were used, other limitations make it impossible to directly compare results and draw the conclusion of an increasing incidence of anti-PEG antibodies in the healthy donor population. These numbers contrast with a report in which about 4 % of 350 healthy blood donors were found antibody-positive using a commercially available ELISA assay. The animal data also show conflicting results concerning the immunogenicity of PEG. In all cases, a PEGylated product was necessary to induce an antibody response; PEG alone was not immunogenic. The immunogenic properties were dependent on the protein and the size and chemical composition of the terminal part of the PEG moiety (40).

Evidence source(s) and strength of evidence:

There was 1 report of serious hypersensitivity in Study APL2-CP-PNH-204. This moderate SAE of hypersensitivity was deemed by the investigator to be related to pegcetacoplan. The event, which occurred on Day 1 (i.e., the subject's 1st day of dosing), led to the subject's discontinuation from the study. The subject was negative for anti pegcetacoplan peptide antibody response before dosing on Day 1; no further monitoring of this subject's anti pegcetacoplan peptide antibody response was performed. In addition to the SAE of hypersensitivity, nonserious TEAEs that could be considered as hypersensitivity reactions, including urticaria, generalized erythema, erythema, pruritus, rash, and rash maculopapular, were observed in this study. 1 subject in this study had a mild TEAE of maculopapular rash deemed by the investigator to be related to pegcetacoplan. This event was temporally associated with positive serum anti-PEG antibodies but not anti pegcetacoplan peptide antibodies. The rash subsequently resolved, and anti-PEG serology became negative despite uninterrupted treatment with pegcetacoplan. These 2 cases of hypersensitivity were treated and resolved.

In Study APL2-302, 18 subjects (22.5 %) treated with pegcetacoplan had an event in the SMQ of Hypersensitivity (9 subjects [11.3 %] had mild events, 6 subjects [7.5 %] had moderate events, and 3 subjects [3.8 %] had severe events), including 2 subjects (2.5 %) experiencing serious hypersensitivity events. Erythema (in 5.0 % of subjects), rhinitis allergic (in 2.5 % of subjects), and acute respiratory failure (in 2.5 % of subjects) were the most common TEAEs in the SMQ of Hypersensitivity. According to medical review, subjects who had acute respiratory failure did not experience hypersensitivity reactions. 5 subjects (6.3 %) had events in the SMQ of

Hypersensitivity that were deemed by the investigator to be related to pegcetacoplan. The PTs were acute respiratory failure (1 event), erythema (1 event), hypersensitivity pneumonia (1 event), mechanical urticaria (1 event), and pruritus (1 event). 3 subjects (3.8 %) had severe events in the SMQ of Hypersensitivity, including 1 subject who had an SAE of hypersensitivity pneumonitis that led to study discontinuation. There was also 1 moderate SAE of allergy to immunoglobulin therapy, from which the subject recovered, and was deemed by the investigator to be unrelated to pegcetacoplan.

In Study APL2-308, 12 subjects (26.1 %) treated with pegcetacoplan had an event in the SMQ of Hypersensitivity. 11 subjects (23.9 %) had mild events and 1 subject (2.2 %) had moderate events; no subjects had severe events. Erythema (in 6.5 % of subjects), rash (in 4.3 % of subjects), and rash maculopapular (in 4.3 % subjects) were the most common TEAEs in the SMQ of Hypersensitivity. 3 subjects (6.5 %) had events in the SMQ of Hypersensitivity that were deemed by the investigator to be related to pegcetacoplan. The PTs were rash (2 events) and rash maculopapular (1 event).

In Study APL2-302, ISRs were frequently reported, although none were severe or serious, and treatment continued in all subjects without sequelae. Across Study APL2-302, in the overall pegcetacoplan monotherapy group (N=80), 29 subjects (36.3 %) had at least 1 ISR. Injection site erythema (in 16.3 % of subjects) was the most commonly reported ISR. Of the 15 subjects who dose-escalated, 1 subject (6.7 %) had an ISR of moderate severity (injection site pain) during or after dose escalation that was deemed by the investigator to be related to pegcetacoplan. All ISRs were mild (26 subjects [32.5 %]) or moderate (3 subjects [3.8 %]) in severity; there were no severe ISRs. There were no treatment discontinuations due to ISRs.

In Study APL2-308, 16 subjects (34.8 %) in the overall pegcetacoplan group had at least 1 ISR. All ISRs were mild in severity; there were no moderate or severe ISRs. Erythema (in 6.5 % of subjects) was the most commonly reported ISR.

In Studies APL2-202, APL2-CP-PNH-204, and APL-CP0514, no ISRs were severe or led to discontinuation.

The risk of serious hypersensitivity reactions is a theoretical potential risk because of the mechanism of action of pegcetacoplan and reports on potential for immunogenicity from PEG.

In the post marketing setting, very limited information was provided for 2 cases of anaphylactic reaction in subjects on pegcetacoplan; however, in both cases, pegcetacoplan treatment was continued, and the events resolved. In addition, 1 case of supposed anaphylactic shock has been reported, which was considered by the company to be related to pegcetacoplan given the plausible temporal relationship and lack of alternate etiologies.

Characterization of the risk:

The risk of serious hypersensitivity reactions is a theoretical risk that is based on the potential of any medicinal product and, specifically, a product structure including a PEG molecule.

In Study APL2-302, 18 subjects treated with pegcetacoplan had an event in the SMQ of Hypersensitivity (9 mild, 6 moderate, and 3 severe). 5 subjects had events in the SMQ of Hypersensitivity that were deemed by the investigator to be related to pegcetacoplan. The PTs

were acute respiratory failure (1 event), erythema (1 event), hypersensitivity pneumonia (1 event), mechanical urticaria (1 event), and pruritus (1 event).

In Study APL2-308, 12 subjects treated with pegcetacoplan had an event in the SMQ of Hypersensitivity (11 mild and 1 moderate). 3 subjects had events in the SMQ of Hypersensitivity that were deemed by the investigator to be related to pegcetacoplan. The PTs were rash (2 events) and rash maculopapular (1 event).

All completed and ongoing clinical studies have evaluated the immunogenicity potential of pegcetacoplan using validated assays for assessment of anti pegcetacoplan peptide antibody and anti-PEG antibody in human serum samples. To date, in 511 patients and 818.36 person-years of systemic pegcetacoplan exposure in ongoing and completed clinical trials, no apparent correlation of antibody development to an altered PK profile has been observed. There has been no observed correlation of ADA development to clinical response or AEs in healthy subjects or subjects with PNH.

In the post marketing setting, very limited information was provided for 2 cases of anaphylactic reaction in subjects on pegcetacoplan; however, in both cases, pegcetacoplan treatment was continued, and the events resolved. In addition, 1 case of supposed anaphylactic shock has been reported, which was considered by the company to be related to pegcetacoplan given the plausible temporal relationship and lack of alternate etiologies.

Risk factors and risk groups:

Patients with a history of hypersensitivity to PEG are considered to have an increased risk of being hypersensitive to pegcetacoplan.

In the pegcetacoplan clinical development program, the immunogenicity potential of pegcetacoplan was assessed by evaluation of samples using validated assays for assessment of anti pegcetacoplan peptide antibody and anti-PEG antibody in human serum samples. There was no apparent correlation of antibody development to an altered PK profile. There has been no observed correlation of ADA development to clinical response or AEs in healthy subjects or subjects with PNH.

Preventability:

Any hypersensitivity to pegcetacoplan should be evaluated carefully, and continuation of treatment plan assessed carefully. Prior hypersensitivity puts patients at risk for serious hypersensitivity reactions.

In the case of a serious hypersensitivity reaction, pegcetacoplan infusion should be immediately discontinued, and appropriate treatment needs to be instituted.

Impact on the risk-benefit balance of the product:

To date, in 511 patients and 818.36 person-years of systemic pegcetacoplan exposure in ongoing and completed clinical trials, no reported cases of anaphylaxis have occurred.

There has been no observed correlation of ADA development to clinical response or AEs in healthy or PNH subjects.

In the post marketing setting, 2 poorly documented cases of anaphylactic reaction in subjects on pegcetacoplan have occurred in 626.58 person-years of systemic pegcetacoplan exposure. These

events resolved while pegcetacoplan was continued. In addition, 1 case of supposed anaphylactic shock has been reported, which was considered by the company to be related to pegcetacoplan given the plausible temporal relationship and lack of alternate etiologies.

No impact from this risk is expected on the risk-benefit balance.

Public health impact:

To date, in 511 patients and 818.36 person-years of systemic pegcetacoplan exposure in ongoing and completed clinical trials, no reported cases of anaphylaxis have occurred.

There has been no observed correlation of ADA development to clinical response or AEs in healthy or PNH subjects.

In the post marketing setting, 2 poorly documented cases of anaphylactic reaction in subjects on pegcetacoplan have occurred in 626.58 person-years of systemic pegcetacoplan exposure. These events resolved while pegcetacoplan was continued. In addition, 1 case of supposed anaphylactic shock has been reported, which was considered by the company to be related to pegcetacoplan given the plausible temporal relationship and lack of alternate etiologies.

No impact from this risk is expected on public health at the population level.

Important potential risk 3:

IVH after drug discontinuation

Potential mechanisms:

The mechanism of IVH after drug discontinuation is the result of the activity of pegcetacoplan in controlling the PNH disease process. Once pegcetacoplan is not present, the complement system attack of PNH RBCs can lead to hemolysis. PNH is characterized by the clonal expansion of HSCs and their progeny, mature blood cells, which carry an acquired somatic mutation in the PIG-A gene. PIG-A codes for an enzyme that is essential for the biosynthesis of the GPI anchor, a protein modification allowing the attachment of proteins to the cell membrane. The preferential expansion of these PIG-A mutated HSCs leads to the release of RBCs into the circulation that lack, among other GPI-anchored proteins, the 2 key complement regulators CD55 and CD59. As a result of this deficiency, PNH erythrocytes are incapable of withstanding physiologic complement activation (because of spontaneous C3 tick-over or bystander activation) and undergo persistent C3 opsonization and terminal pathway activation that culminate in MAC-mediated IVH (42).

Pegcetacoplan binds to human C3 and C3b, resulting in proximal inhibition of the complement cascade. It inhibits the activity of the alternative complement pathway, which protects the PNH RBCs from hemolysis. The PNH erythrocytes cannot properly curb complement activation on their surface that leads to IVH and EVH (42).

This was demonstrated in the clonal distribution data for pegcetacoplan in the pivotal clinical study, Study APL2-302.

The bone marrow of patients with PNH contains 2 distinct populations of clonal HSCs (PIG-A deficient and PIG-A competent) that give rise to all blood elements, namely RBCs, white blood cells, and platelets. RBCs issued from the PIG-A deficient mutant clonal population within the bone marrow are particularly sensitive to complement-mediated lysis (55).

Measurement of the proportion of monocytes lacking a GPI anchor (i.e., fluorescein-labeled proaerolysin negative) is believed to correlate with the proportion of the bone marrow populated by PIG-A deficient stem cell clones (i.e., PNH clonal population). However, measurement of the proportion of RBCs lacking a GPI anchor (i.e., CD59 dim [Type II] and CD59-deficient [Type III]; PNH RBCs) normally shows a disproportionally reduced proportion of PNH RBCs because of the ongoing hemolysis that destroys these cells in the interval between their production by the bone marrow and their measurement by flow cytometry. An intervention that protects PNH RBCs from hemolytic destruction will cause the proportion of PNH RBCs to increase. A proportion of PNH RBCs (Type II and Type III) that matches the proportion of PNH monocytes indicates that little hemolysis is taking place and that the proportion measured is likely to reflect the production of both types of RBCs by the bone marrow (normal Type I RBCs versus PNH [Type II and Type III] RBCs) (55).

In Study APL2-302, as expected, the proportions of PNH granulocytes and monocytes did not change during the course of the study in either treatment group. The percentages of clonal distribution of PNH Type II and Type III RBCs increased from 66.80 % at baseline to 93.85 % at Week 16 with pegcetacoplan treatment, which was maintained to Week 48. PNH Type II and Type III RBCs was close to 90 % at Week 48 for subjects in both the pegcetacoplan/ pegcetacoplan group and the eculizumab/pegcetacoplan group, indicating similar efficacy in both treatment arms. This increase in Type III PNH RBCs after pegcetacoplan indicates a reduction in hemolysis and protection of the PNH RBCs, corresponding to the rise in Hb levels. The sum of mean clonal distribution of PNH RBCs (percentage PNH Type II + Type III) was close to 90 % of overall PNH RBCs at Week 48 for subjects in both the pegcetacoplan group and the eculizumab group. This is similar to the percentage of FLAER observed for PNH monocytes, suggesting that repeated dosing of pegcetacoplan can preserve PNH Type II and Type III cells in PNH patients by preventing hemolysis. The percentage of PNH Type II and III cells with C3d decreased from 17.73 % at baseline to 0.20 % at Week 16 with pegcetacoplan treatment, which was maintained to Week 48. The eculizumab/pegcetacoplan group had a consistently high percentage of PNH Type II and III cells with C3d deposition at baseline (19.82 %) and at Week 16 (16.94 %) during treatment with eculizumab, consistent with ongoing IVH despite C5i-therapy. This was reduced to 0.07 % after treatment with pegcetacoplan monotherapy. For subjects in the eculizumab/pegcetacoplan group, there was a decrease in C3 deposition on Type II and III RBCs after switching to dosing of pegcetacoplan at Week 17. At Week 48, the percentages of C3 deposition on Type I PNH, Type II PNH, and Type III PNH RBCs for subjects in eculizumab/pegcetacoplan group were similar to those in pegcetacoplan group. C3 deposition is an indicator of opsonization and EVH, suggesting that pegcetacoplan protects Type II and III PNH cells from complement-mediated attack and EVH.

Evidence source(s) and strength of evidence:

The PNH disease process and mechanism of control for it by complement inhibition is the source of this risk. Inhibition of complement C3 protects circulating RBCs, produced by mutant stem cell clones, from hemolysis. Discontinuation of treatment risks acute hemolytic crisis because of these RBCs becoming vulnerable to destruction in patients with PNH (28).

Characterization of the risk:

IVH is a known potential risk when complement inhibition is stopped in patients with PNH.

Hemolysis occurring in study subjects after sudden pegcetacoplan withdrawal has been observed. In Study APL2-204, 1 subject had pegcetacoplan administration withheld by the investigational site for 8 days, without consultation with the study sponsor, because of a herpes zoster infection. The subject was instructed by the investigator to resume administration immediately and received pegcetacoplan on the next 2 days. On the following day, the subject withheld pegcetacoplan dosing because of abdominal discomfort and was subsequently diagnosed with severe hemolysis. The gap in this subject's pegcetacoplan dosing was associated with the onset of hemolysis.

In Study APL2-CP0514, pegcetacoplan treatment was temporarily ceased for 1 subject following an SAE of alanine aminotransferase increased. 20 days later, the subject had an SAE of anemia that was attributed to rebound hemolysis following cessation of pegcetacoplan treatment.

In the RCP of Study APL2-302, some hemolytic events occurred in the eculizumab group for which the investigator assessed the causal relationship to the study drug as possibly or definitely related to pegcetacoplan. It should be noted that subjects were not receiving pegcetacoplan during the RCP, but the investigator attributed the event to the discontinuation of pegcetacoplan after the run-in period. No events of hemolysis occurred because of missed or delayed pegcetacoplan or eculizumab doses.

In Study APL2-302, no hemolytic disorders occurred during the run-in periods; however, 1 subject (1.3 %) had a severe SAE of hemolysis on Study Day 13 prior to starting eculizumab monotherapy. Although this event occurred during the RCP, it is categorized under the run-in period because the 1st dose of eculizumab monotherapy was given on Study Day 15, which was after the event occurred and considered during "pegcetacoplan + eculizumab" therapy. Overall, 22 subjects (27.5 %) treated with pegcetacoplan had an event in the SMQ of Haemolytic disorders (1 subject [1.3 %] had a mild event, 9 subjects [11.3 %] had moderate events, and 12 subjects [15.0 %] had severe events), including 8 subjects (10.0 %) experiencing serious hemolytic events. Hemolysis (in 19 subjects [23.8 %]) was the most common TEAE in the SMQ of Haemolytic disorders. 3 subjects (3.8 %) experienced hemolysis that was deemed by the investigator to be related to pegcetacoplan. As a result of the hemolytic events, the dose of pegcetacoplan was increased in 10 subjects, and the study drug was withdrawn in 5 subjects. In the RCP, TEAEs of hemolysis occurred less frequently in the pegcetacoplan group (5 subjects [12.2 %]) than in the eculizumab group (14 subjects [35.9 %]). This suggests that no additional risk for hemolysis is associated with pegcetacoplan treatment.

In Study APL2-308, no hemolytic disorders were reported during the RCP. In the post-RCP, 2 subjects (5.7 %) treated with pegcetacoplan had an event in the SMQ of Haemolytic disorders (1 subject [2.2 %] had a moderate event of hemolysis and 1 subject [2.2 %] had a severe event of breakthrough hemolysis). 1 additional subject (9.1 %) in the standard of care to pegcetacoplan group experienced a moderate event of hemolysis. In all 3 instances, the events resulted in a dose increase.

In the post marketing setting, there has been one report of hemolysis that occurred after pegcetacoplan discontinuation. In this case, the hemolytic event was most likely associated with the underlying PNH. Symptoms resolved in 1 to 2 days after treatment with pegcetacoplan was resumed.

Risk factors and risk groups:

Patients with PNH who are being treated with a complement inhibitor and who have not been established on an effective alternative therapy at the time of discontinuation of a complement inhibitor are at higher risk for IVH after drug discontinuation.

Preventability:

If patients with PNH discontinue treatment with pegcetacoplan, they should be closely monitored for signs and symptoms of serious IVH. Serious IVH is identified by elevated LDH levels along with a sudden decrease in PNH clone size or Hb, or reappearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, dyspnea, MAVE (including thrombosis), dysphagia, or erectile dysfunction. If discontinuation of this medicinal product is necessary, alternate therapy should be considered. If serious hemolysis occurs after discontinuation, consider the following procedures/treatments: blood transfusion (packed RBCs), exchange transfusion, anticoagulation, and corticosteroids. Patients should be closely monitored for at least 8 weeks from the last dose, representing more than 5 half-lives of pegcetacoplan, to allow for pegcetacoplan washout and to detect serious hemolysis and other reactions after discontinuation. In addition, slow weaning should be considered.

Impact on the risk-benefit balance of the product:

In Study APL2-CP0514, pegcetacoplan treatment was temporarily ceased for 1 subject following an SAE of alanine aminotransferase increased. 20 days later, the subject had an SAE of anemia that was attributed to rebound hemolysis following cessation of pegcetacoplan treatment.

In Study APL2-CP-PNH-204, 1 subject had pegcetacoplan administration withheld by the investigational site for 8 days, without consultation with the study sponsor, because of a herpes zoster infection. The subject was instructed by the investigator to resume administration immediately and received pegcetacoplan on the next 2 days. On the following day, the subject withheld pegcetacoplan dosing because of abdominal discomfort and was subsequently diagnosed with severe hemolysis. The gap in this subject's pegcetacoplan dosing was associated with the onset of hemolysis.

In Study APL2-302, no hemolytic disorders occurred during the run-in periods; however, 1 subject (1.3 %) had a severe SAE of hemolysis on Study Day 13 prior to starting eculizumab monotherapy. Although this event occurred during the RCP, it is categorized under the run-in period because the 1st dose of eculizumab monotherapy was given on Study Day 15, which was after the event occurred and considered during "pegcetacoplan + eculizumab" therapy. Overall, 22 subjects (27.5 %) treated with pegcetacoplan had an event in the SMQ of Haemolytic disorders (1 subject [1.3 %] had a mild event, 9 subjects [11.3 %] had moderate events, and 12 subjects [15.0 %] had severe events), including 8 subjects (10.0 %) experiencing serious hemolytic events. Hemolysis (in 19 subjects [23.8 %]) was the most common TEAE in the SMQ of Haemolytic disorders. 3 subjects (3.8 %) experienced hemolysis that was deemed by the investigator to be related to pegcetacoplan. As a result of the hemolytic events, the dose of pegcetacoplan was increased in 10 subjects, and the study drug was withdrawn in 5 subjects. In the RCP, TEAEs of hemolysis occurred less frequently in the pegcetacoplan group (5 subjects [12.2 %]) than in the eculizumab group (14 subjects [35.9 %]). This suggests that no additional risk for hemolysis is associated with pegcetacoplan treatment.

In Study APL2-308, no hemolytic disorders were reported during the RCP. In the post-RCP, 2 subjects (5.7 %) treated with pegcetacoplan had an event in the SMQ of Haemolytic disorders (1 subject [2.2 %] had a moderate event of hemolysis and 1 subject [2.2 %] had a severe event of breakthrough hemolysis). 1 additional subject (9.1%) in the standard of care to pegcetacoplan group experienced a moderate event of hemolysis. In all 3 instances, the events resulted in a dose increase.

In the post marketing setting, there has been one report of hemolysis that occurred after pegcetacoplan discontinuation. Symptoms resolved in 1 to 2 days after treatment with pegcetacoplan was resumed.

Public health impact:

Pegcetacoplan adds an efficacious treatment option for PNH in controlling both IVH and EVH. Thus, the public health impact is expected to be positive.

Important potential risk 4:

Immunogenicity

Potential mechanisms:

As with all therapeutic proteins, autoantibodies may develop against pegcetacoplan. The exact mechanism is not known.

Evidence source(s) and strength of evidence:

Immunogenicity is a known potential of all medicinal products and is a class effect of all therapeutic peptides and proteins. No significant data have been identified for risk factors for immunogenicity in patients with PNH, neither within the conducted clinical trials for PNH nor identified in further publicly available articles or literature related to immunogenicity or antibodies to drug.

Characterization of the risk:

Infrequent and generally transient anti pegcetacoplan peptide antibody responses have been detected in pegcetacoplan-treated subjects across all clinical studies. The incidence of anti pegcetacoplan peptide antibodies was low; when it occurred, the titer value was low. A high percentage of preexisting anti-PEG antibody responses has been reported in the predose samples. However, low incidences of treatment-emergent or treatment-boosted anti-PEG antibody response were observed across all clinical studies, and many of those responses were transient. These ADA responses had no noticeable impact on the PK/PD, efficacy, or safety profile of pegcetacoplan.

An NAb assay was not developed to test samples positive for anti-PEG antibody because the PEG portion of the molecule is not the active moiety for mechanism of action. Furthermore, ADA to either the PEG or the active moiety of pegcetacoplan were selected as covariates of interest for evaluation of PK parameters of pegcetacoplan in population PK analysis. The results demonstrated that ADA (to either PEG or the active moiety) had no statistically significant impact on the PK parameters of pegcetacoplan.

In Study APL2-308, of the 46 subjects who received at least 1 dose of pegcetacoplan, 38 tested positive for anti-PEG antibodies. Of these, 7 developed a treatment-emergent response, and 5 developed a treatment-boosted response. Of the subjects treated with standard of care,

1 subject developed a treatment-emergent anti-PEG response, and 3 subjects developed a treatment-boosted anti-PEG response.

In Study APL2-302, all subjects received 4 weeks of s.c. dosing of pegcetacoplan during the run-in period. At Week 16, no subjects randomized to the pegcetacoplan group tested positive for anti pegcetacoplan peptide during the RCP. 2 subjects randomized to the eculizumab group tested positive at titers of 1:10; both subjects' test results were confirmed as positive in NAb assay. No trend of reduction in systemic pegcetacoplan exposure or clinical efficacy was observed in both subjects. The therapeutic effect of pegcetacoplan was maintained through Week 16. There were no reports of anti pegcetacoplan antibody during the OLP. The results indicate that there was no discernible effect of the neutralizing capability of the ADAs on PK or clinical efficacy. Testing for anti pegcetacoplan peptide antibody response in all other visits prior to and after Week 16 was negative for both subjects.

No samples tested positive for anti pegcetacoplan peptide antibodies in Study APL2-202 and Study 102.

2 samples tested positive for anti pegcetacoplan peptide antibodies in Study APL2-CP-PNH-204. Both samples were negative for NAb analysis.

1 sample tested positive for anti pegcetacoplan peptide antibodies in Study 205. The sample was the Day 1 predose sample before the 1st administration of pegcetacoplan. Because this Day 1 predose sample was the only sample positive for ADA in this study, NAb testing was not performed for this study. However, the PK profile for this subject was similar to those of other subjects in the study.

3 samples tested positive for anti pegcetacoplan peptide antibodies in Study 101:

- The Day 84 sample for a subject tested positive for ADA with a titer of <1:10 and also tested positive in the NAb analysis. Day 84 was the last regular visit for the study. A follow-up sample obtained 550 days after End of Visit (Day 84) tested negative for anti pegcetacoplan peptide antibody. The PK profile for this subject was similar to those of others in the same cohort.
- The Day 84 sample for another subject tested positive for ADA with a titer of 1:10 and also tested positive in the NAb analysis. A follow-up sample could not be obtained because the subject moved geographically, and it was not practical to obtain a poststudy blood sample. The PK profile for this subject was similar to others in the same cohort.
- The Day 1 predose sample in a third subject tested positive for ADA with a titer of 1:10 but subsequently tested negative in the NAb analysis. The assessment of NAb results on clinical efficacy is N/A to Study 101 because it is a healthy volunteer study.

In the post marketing setting, there have been no cases involving anti pegcetacoplan antibodies and/or anti-PEG antibodies.

Risk factors and risk groups:

In the pegcetacoplan clinical development program, the immunogenicity potential of pegcetacoplan was assessed by evaluation of samples using validated assays for assessment of anti pegcetacoplan peptide antibody and anti-PEG antibody in human serum samples. There was no apparent correlation of antibody development to an altered PK profile. There has been no

observed correlation of ADA development to clinical response or AEs in healthy subjects or subjects with PNH.

Preventability:

Due to the nature of these events, it is unlikely that they can be prevented. Appropriate information is included in the proposed SmPC.

Impact on the risk-benefit balance of the product:

Patients with persistent high-titer ADAs may be at risk for loss of efficacy. There has been no observed correlation between ADA development and loss of efficacy or AEs in pegcetacoplan studies in healthy or PNH subjects.

No impact from this risk is expected on the risk-benefit balance.

Public health impact:

There has been no observed correlation of ADA development to clinical response or AEs in healthy subjects or subjects with PNH.

No impact from this risk is expected on public health at the population level.

Important potential risk 5:

Malignancies and hematologic abnormalities

Potential mechanisms:

Malignancies

The complement system is involved in the immune editing of malignancies and can play an active protumorigenic role in tumor progression. Chronic inflammation promoted by complement proves to be protumorigenic at different levels – promoting cell death and compensatory proliferation; inducing Tregs, which impair cancer immunity; and promoting immune-suppressive myeloid environment (myeloid-derived suppressor cells, neutrophils, etc). However, the complement system may also promote acute inflammation and participate in mechanisms of immune surveillance directly targeting tumor cells at the early stages of tumor development. It may also be a key player in promoting complement-dependent cytotoxicity-mediated killing of cancer cells (43).

Hematologic abnormalities

PNH is an acquired, clonal, nonmalignant hematologic disease characterized by complement-mediated RBC hemolysis with or without hemoglobinuria, an increased susceptibility to thrombotic episodes, and/or some degree of bone marrow dysfunction (8). PNH is caused by complement-mediated lysis of erythrocyte clones lacking functional CD55 and CD59 on their surface to protect them against this process. As such, these erythrocytes are particularly susceptible to the formation of the MAC and have been shown to lyse readily in the presence of complement activation (8).

Evidence source(s) and strength of evidence:

Prior experience of PNH patients treated with C5 inhibitors and review of published data describing the risk of malignancies and hematologic abnormalities in patients with congenital complement deficiencies is the main reason for including this as an important potential risk.

In clinical trials of eculizumab, the blood and lymphatic system disorders leukopenia and anemia were common (≥1/100 to <1/10), and thrombocytopenia and lymphopenia were uncommon (≥1/1000 to <1/100). Malignancies have been reported in patients with PNH at a rate of 2.6 reports per 100 patient-years (38). However, increase in the incidence of malignancies with the use of eculizumab has not been established. Neoplasms benign, malignant and unspecified were rare (≥1/10 000 to <1/1000; Soliris, Alexion Pharmaceuticals) with eculizumab treatment. In post marketing assessments of the safety of eculizumab, the reporting rate for solid tumors remained stable over time at approximately 0.6 per 100 patient-years (38).

Characterization of the risk:

Malignancies

The occurrence of all TEAEs in the SOC of Neoplasms, Benign, Malignant and Unspecified (including Cysts and Polyps) was low for pegcetacoplan-treated subjects in the PNH studies.

No malignancies were reported in Study APL2-308.

In Study APL2-302, 2 subjects (2.5 %) experienced a moderate TEAE of basal cell carcinoma. 1 subject experienced a severe TEAE of acute myeloid leukemia, and 1 subject experienced a severe TEAE of diffuse large B cell lymphoma. These events were not deemed by the investigator to be related to pegcetacoplan. 1 subject experienced a mild TEAE of skin papilloma, which was deemed by the investigator to be related to pegcetacoplan.

In Study APL2-CP-PNH-204 Cohort 2, 1 (5.0 %) subject experienced a severe SAE of abdominal neoplasm, deemed by the investigator to be unrelated to pegcetacoplan. The event of abdominal neoplasm led to withdrawal of pegcetacoplan. Neither event was resolved by the end of the treatment period.

In the post marketing setting, there have been no cases of malignancy related to pegcetacoplan use reported.

Hematologic abnormalities

A review of all TEAEs in the SOC of Blood and Lymphatic System Disorders in Study APL2-302, Study APL2-202, Study APL2-CP-PNH-204, and Study APL2-CP0514 revealed an incidence of 0 % in Study APL2-202 (n=4), an incidence of 30.0 % in Study APL2-CP-PNH-204 (n=20), an incidence of 16.7 % in Study APL2-CP0514 for pegcetacoplan, an incidence of 38.8 % for pegcetacoplan in Study APL2-302, and an incidence of 21.7 % for pegcetacoplan in Study APL2-308.

During Study APL2-302, 22 subjects (27.5 %) had a hemolytic disorder (12 subjects had severe events, 9 subjects had moderate events, and 1 subject had at least 1 mild event). 8 subjects experienced an SAE within the SMQ of Haemolytic disorders. Hemolysis was the most common TEAE (19 subjects [23.8 %]). 3 subjects each had an event of hemolysis that was determined to be related to the study drug. As a result of the hemolytic events, the dose of pegcetacoplan was

increased in 10 subjects, and the study drug was withdrawn in 5 subjects. Subjects also had events of hemolytic anemia (2 subjects [2.5 %]; 1 SAE that was determined to be possibly related to the study drug), hemoglobin, anemia, hemoglobinuria, and IVH (all in 1 subject).

In Study APL2-308, no hemolytic disorders were reported during the RCP. In the post-RCP, 2 subjects (5.7 %) treated with pegcetacoplan had an event in the SMQ of Haemolytic disorders (1 subject [2.2 %] had a moderate of hemolysis and 1 subject [2.2 %] had a severe event of breakthrough hemolysis). 1 additional subject (9.1 %) in the standard of care to pegcetacoplan group experienced a moderate event of hemolysis. In all 3 instances, the events resulted in a dose increase.

In the post marketing setting, there has been one report of hemolysis that occurred after pegcetacoplan discontinuation. In this case, the hemolytic event was most likely associated with the underlying PNH. Symptoms resolved in 1 to 2 days after treatment with pegcetacoplan was resumed.

Risk factors and risk groups:

None identified.

Preventability:

Not known.

Impact on the risk-benefit balance of the product:

In Study APL2-302 RCP, the safety profile of pegcetacoplan was similar to eculizumab. Pegcetacoplan has the potential to address the underlying disease pathophysiology of PNH and provide benefit in this disease, which has a high unmet medical need. In Study APL2-308, pegcetacoplan was well tolerated, and safety findings in this study were consistent with the known safety profile of pegcetacoplan. Overall, the clinical development program for PNH has shown that pegcetacoplan produces consistent and meaningful effects on relevant clinical efficacy measures and has a manageable safety profile. Therefore, the benefits of pegcetacoplan outweigh the risks.

Public health impact:

There is no public health impact because there is no evidence of an increased risk.

Important potential risk 6:

Potential long-term effects of PEG accumulation

Potential mechanisms:

The risk of potential long-term effects of PEG accumulation is based on the inclusion of a PEG molecule in the product structure (see Chemical class).

There are hypothetical concerns regarding potential long-term risks associated with PEG exposure and related vacuolation in certain vital tissues/structures such as CNS neurons, circumventricular organs, or the choroid plexus (56, 57).

PEG has very low toxicity and, because of its simple structure, is assumed to be of low immunogenicity (40).

Evidence source(s) and strength of evidence:

Preclinical findings from nonclinical studies of pegcetacoplan in rabbits and monkeys are the main reasons for including this as an important potential risk.

In general, PEG-associated cytoplasmic vacuolation has been considered an adaptive tissue response to long-chain PEG, which is widely considered a nonadverse finding, if not accompanied by evidence of cellular distortion, necrosis, degeneration, inflammation, or disturbed body function (57). The only exception is represented by the kidney, in which epithelial degeneration was observed. Short-term safety of PEG has been studied extensively without identification of toxicity beyond reports of renal tubular cell vacuolation and degeneration at very high-dose levels. In some instances, vacuolation was significant, thus leading to tissue distortion, but yet without demonstrated adverse functional outcomes.

Characterization of the risk:

The effects of the PEG moiety in pegcetacoplan were carefully evaluated in the nonclinical studies in rabbits and monkeys. Pegcetacoplan evoked microscopic epithelial vacuolation and infiltrates of vacuolated macrophages in multiple tissues (including kidney and CNS) in both species. Vacuolation was seen at doses ≥1 mg/kg/day in rabbits and ≥7 mg/kg/day in monkeys, and incidence tended to increase with dosage. They are attributed to the PEG40 moiety of pegcetacoplan because (1) they occurred at similar degrees and incidences in parallel animal groups given an equivalent dose of PEG40 alone and (2) their appearance and distribution closely match effects as described for other long-chain PEGs and PEGylated proteins (57, 58).

These changes have been reported with numerous other PEGylated peptide/protein pharmaceuticals, including marketed ones. They are widely considered to represent an adaptive tissue response to long-chain PEG and are regarded as nonadverse, provided that they are not accompanied by evidence of cellular distortion, necrosis, degeneration, inflammation, or disturbed body function (57). In the pegcetacoplan toxicology studies, there was no evidence of these features in any of the tissues in which vacuolation was observed (excepting degeneration in the kidney), and no abnormal clinical signs suggestive of disturbed function were observed.

Renal degeneration was noted in the chronic nonhuman primate study; it was minimal and nonprogressive but considered adverse at 28 mg/kg/day. The severity and extent of the renal degeneration noted did not change when the 28-day study and the 9-month studies were compared. Importantly, the foci of renal tubular degeneration are spatially associated with, and thus considered related to, the renal vacuolation. In further support of that, such foci were also observed co-located with vacuolation in the PEG40-alone groups in the chronic studies, implicating the PEG40 moiety in these microscopic changes. Therefore, consistent with the literature on PEG-related vacuolation, the foci of renal degeneration are considered likely to resolve with resolution of the vacuolation.

Regarding the choroid plexus (ependymal) epithelium, it is also noteworthy that there were no clinical signs suggestive of disturbed neurobehavioral function. Accordingly, the tissue vacuolation observed with pegcetacoplan is considered nonadverse, except for the kidney, in which epithelial degeneration was observed. Overall, the chronic rabbit and nonhuman primate studies demonstrated expected PEG-related findings, which are anticipated to be reversible, given sufficient time, and which were not associated with any functional alterations.

A distribution and excretion study was conducted in monkeys using radiolabeled pegcetacoplan (Study 17MTX-001). This study showed broad distribution to multiple tissues and renal excretion. The radiolabel was attached to the peptide portion of the drug, so this study does not specifically inform distribution and tissue kinetics of the PEG portion. Therefore, an estimation of specific tissue accumulation and clearance of PEG cannot be estimated from this study.

Safety signals that could arise from exposure to PEG40 moiety of pegcetacoplan have had special focus in the safety assessment of pegcetacoplan and have been investigated in clinical studies. The intention has been to identify adverse findings that, theoretically, could be related to the function of excretory organs, such as the kidney, liver, and choroid plexus. Throughout the clinical development of pegcetacoplan, no increase of potentially PEG-associated events (nervous system, renal, and hepatic disorders) was noted over time. Additionally, creatinine levels have been monitored in the clinical trials of pegcetacoplan because creatinine level is a commonly used endogenous marker for the assessment of glomerular function.

In Study APL2-302, mean values and CFB in serum creatinine concentrations were also similar in the eculizumab and pegcetacoplan groups during the RCP. Mean creatinine values showed no meaningful changes over time and generally stayed within the normal range in both groups at all time points during the study up to 48 weeks. There was no meaningful change in mean creatinine levels in PNH subjects after treatment with pegcetacoplan for 48 weeks. In Study APL2-308, mean creatinine values showed no meaningful changes over time and generally stayed within the normal range in both groups at all time points during the study. No other signal with regard to renal function has been detected in the current cumulative clinical safety database for pegcetacoplan.

In the post marketing setting, there is no evidence of the effects of the long-term accumulation of PEG in pegcetacoplan impacting the liver or kidneys.

Risk factors and risk groups:

None identified.

Preventability:

PEG-related microscopic vacuolation is generally considered reversible over a period of months. Reversibility was not demonstrated in the pegcetacoplan animal studies after 1 month and was not evaluated for a longer duration.

Impact on the risk-benefit balance of the product:

No impact from this risk is expected on the risk-benefit balance as there is no evidence of an increased risk.

Public health impact:

Public health impact from this risk is low.

SVII.3.2. Presentation of the missing information

Missing information:

Use in patients with BMF

Evidence source:

Use of pegcetacoplan in patients with BMF (low population of blood stem cells) has not been evaluated because these subjects were excluded from PNH clinical trials in the clinical development program. Therefore, the risk for this population is unknown, and there is currently no evidence that could rule out a potential risk.

In the post marketing setting, there have been 4 cases in subjects with aplastic anemia who experienced adverse drug reactions. The reported events were reflective of the underlying disease of aplastic anemia and PNH.

Population in need of further characterization:

Limited information is available on the risk profile of individuals with BMF who are treated with pegcetacoplan; therefore, this population is in need of further characterization.

Use in pregnant women

Evidence source:

Use of pegcetacoplan in pregnant women has not been evaluated because these subjects were excluded from PNH clinical trials in the clinical development program.

1 pregnancy was reported during the pegcetacoplan development program in a female subject in Study APL2-CP0514. Administration of pegcetacoplan to this subject was immediately stopped following laboratory confirmation of the pregnancy. At the time pegcetacoplan was discontinued, the subject was approximately 5 weeks' pregnant. Antenatal ultrasound scans were normal, and the subject delivered a full-term baby with no complications reported during delivery. No abnormalities were reported with regard to the infant's health.

In Study APL2-308, there were no pregnancies reported in women treated with pegcetacoplan; however, 1 pregnancy was reported in the female partner of a male subject treated with pegcetacoplan in this study. The pregnancy resulted in spontaneous abortion at approximately 6 weeks' gestation.

In the post marketing setting, 3 pregnancies have been reported. The 1st concerned a multiparous female with PNH and a medical history of 2 previous failed pregnancies while taking eculizumab. The patient became pregnant approximately 5 months after starting treatment with pegcetacoplan. At 30 weeks' gestation, the patient was admitted to the intensive care unit due to placental abruption and developed postpartum breakthrough hemolysis. The patient's baby was delivered via Cesarean section and was admitted to the neonatal intensive care unit; the baby was doing well. The 2nd concerned a female with PNH whose urine pregnancy test was positive less than a month after pegcetacoplan treatment initiation. No further information was provided. The 3rd concerned a female of unknown age who became pregnant and discontinued treatment with pegcetacoplan. No further information was provided.

There are insufficient data on pegcetacoplan use in pregnant women to inform a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes up to the data cut-off date (13 November 2023).

Therefore, pegcetacoplan should not be given to pregnant women at this time. Women of childbearing potential should use effective contraception methods to prevent pregnancy during treatment with pegcetacoplan and for at least 8 weeks after the last dose of pegcetacoplan.

There are no data on the effects of pegcetacoplan on human milk production through the data cut-off date (13 November 2023).

Minimal (less than 1 %, not pharmacologically significant) pegcetacoplan excretion in milk has been demonstrated in monkeys; therefore, the probability of clinically relevant exposure of breastfed infants through breastmilk is considered minimal. However, because human complement is present in human milk and the potential for absorption and harm to the infant is unknown, physicians should consider the benefits of breastfeeding along with the mother's clinical need for pegcetacoplan and potential risks for the breastfeeding child.

Population in need of further characterization:

Limited information is available on the risk profile of pregnant women being treated with pegcetacoplan; therefore, this population is in need of further characterization.

Any pregnant woman exposed to pegcetacoplan.

Long-term safety (>1 year)

Evidence source:

Study APL2-307 is an ongoing study and, as of 13 November 2023, there were 137 patients in the safety dataset with a mean duration of treatment of 975.2 days (standard deviation 352.81 days). No new safety signals were identified during the reporting period of long-term treatment.

In the post marketing setting, 28 cases were identified in subjects who were treated with pegcetacoplan for >1 year. The nature of reported events from these cases was reflective of the known high morbidity of PNH and its known frequent complications; no particular pattern of events was observed.

There are limited data on long-term safety of pegcetacoplan in patients with PNH.

Population in need of further characterization:

Limited information is available on the risk profile of long-term use of pegcetacoplan in patients with PNH; therefore, this population is in need of further characterization. The long-term safety of pegcetacoplan in patients with PNH will be monitored in the Sobi.PEGCET-301 PASS and Study APL2-307 (see Part III).

Part II: Module SVIII - Summary of the safety concerns

Table 9 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	1. Serious infections 2. Serious hypersensitivity reactions 3. IVH after drug discontinuation 4. Immunogenicity 5. Malignancies and hematologic abnormalities 6. Potential long-term effects of PEG accumulation
Missing information	1. Use in patients with BMF 2. Use in pregnant women 3. Long-term safety (>1 year)

Abbreviations: BMF, Bone marrow failure; IVH, Intravascular hemolysis; PEG, Polyethylene glycol.

Part III: Pharmacovigilance plan

III.1 Routine pharmacovigilance activities

There are no routine pharmacovigilance activities beyond adverse reactions reporting or signal detection.

III.2 Additional pharmacovigilance activities

Study short name and title:

PASS of pegcetacoplan in patients with PNH (Study Sobi.PEGCET-301)

Rationale and study objectives:

The purpose of this study is to gain more data on the long-term safety profile of pegcetacoplan and evaluate if the use of pegcetacoplan in adult patients with PNH increases the risk of certain adverse outcomes.

The primary objective is to evaluate the occurrence of serious infections in patients with PNH treated with pegcetacoplan.

Secondary objectives are:

- To characterize the long-term safety profile of pegcetacoplan in patients with PNH.
- To evaluate additional risk minimization measures (guide for healthcare professionals, patient card, patient/carer guide, prescriber checklist, and annual revaccination reminders to the prescribers).
- To assess adherence to label requirements regarding routine risk minimization measures for the important potential risk “serious infections”.
- To characterize safety profile in patient with BMF (as available).
- To evaluate long-term potential effects of PEG accumulation in kidney and liver.

Study design:

Sobi.PEGCET-301 will use data extracted from the Sobi.PEGCET-304 study database.

Sobi.PEGCET-304 is an observational study designed to describe the real-world effectiveness of pegcetacoplan in patients with PNH. Sobi.PEGCET-304 is currently ongoing and is collecting both retrospective and prospective data with the main part being prospective, collecting data on effectiveness, safety (all adverse events), patient- and clinician-reported outcomes and health care resource use.

Sobi.PEGCET-304 is observational and will not affect the patient and investigator relationship, nor influence the investigator’s drug prescription or therapeutic management of the patient. The decision to treat patients with pegcetacoplan will be independent from the decision to enroll patients in the study.

Study population:

Patients included in study Sobi.PEGCET-304 (target sample size n=200).

Milestones:

Submission of protocol: Within 6 months of approval of synopsis (submitted 13 June 2022)

Submission of protocol amendment: Q4 2024

Start of data collection: Q3 2023

End of data collection: Q3 2029

Progress report: Within the PSUR

Final study report: estimated Q1 2030

Study short name and title:

A long-term extension study for patients with PNH (Study APL2-307)

An open-label, nonrandomized, multicenter extension study to evaluate the long-term safety and efficacy of pegcetacoplan in the treatment of PNH

Rationale and study objectives:

This extension study protocol was developed to continue evaluation of the long-term safety and efficacy of pegcetacoplan in subjects with PNH.

The objectives of this study are to:

- Establish the long-term safety of pegcetacoplan in subjects with PNH
- Establish the long-term efficacy of pegcetacoplan in subjects with PNH

Study design:

This study is an open-label, non-randomized, multicenter extension phase 3 study.

Study population:

Subjects who have completed other pegcetacoplan PNH clinical trials are eligible to participate in this trial.

Milestones:

Final report: Q2 2026

III.3 Summary table of additional pharmacovigilance activities

Table 10 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities *(by the competent authority)*				
PASS Sobi.PEGCET-301	To evaluate the occurrence of serious infections in patients with PNH treated with pegcetacoplan	• Serious infections • Serious hypersensitivity reactions • IVH after drug discontinuation • Immunogenicity • Malignancies and hematologic abnormalities • Potential long-term of effects of PEG accumulation • Use in patients with BMF • Long-term safety (>1 year)	Submission of final protocol: Submission of protocol amendment: Start of data collection: End of data collection: Progress report: Final study report:	Within 6 months of synopsis approval (submitted 13 June 2022) Q4 2024 June 2023 Q3 2029 Within the PSUR Q1 2030

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study APL2-307 Ongoing	To evaluate the long-term safety and efficacy of pegcetacoplan in subjects with PNH	• Serious infections • Serious hypersensitivity reactions • IVH after drug discontinuation • Immunogenicity • Malignancies and hematologic abnormalities • Potential long-term effects of PEG accumulation • Long-term safety (>1 year)	Final report:	Q2 2026

Abbreviations: BMF, Bone marrow failure; IVH, Intravascular hemolysis; N/A, Not applicable; PASS, Post authorization safety study; PEG, Polyethylene glycol; PNH, Paroxysmal nocturnal hemoglobinuria; PSUR, Periodic Safety Update Report: Q, Quarter.

Part IV: Plans for post authorization efficacy studies

No post authorization efficacy studies are planned.

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk minimization plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine risk minimization measures

Table 11 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important potential risks	
Serious infections	• SmPC: Section 4.3, Section 4.4, and Section 4.8 • Package Leaflet: Section 2, Section 3, and Section 4 Recommendation for monitoring patients and informing them of signs and symptoms is included in the SmPC under Section 4.4.
Serious hypersensitivity reactions	• SmPC: Section 4.3 and Section 4.4 • Package Leaflet: Section 2 Recommendation for discontinuation of pegcetacoplan and instituting appropriate treatment is included in the SmPC Section 4.4.
IVH after drug discontinuation	• SmPC: Section 4.2 and Section 4.4 • Package Leaflet: Section 2, Section 3, and Section 4 Recommendation for monitoring patients for signs and symptoms is included in the SmPC. If discontinuation of pegcetacoplan is necessary, alternate therapy should be considered because PNH is life-threatening if untreated. In addition, slow weaning should be considered, and patients should carefully be monitored for at least 8 weeks to detect serious hemolysis and other reactions as alternative complement inhibitors may not prevent hemolysis as efficiently.
Immunogenicity	• SmPC: Section 4.8
Malignancies and hematologic abnormalities	• None
Potential long-term effects of PEG accumulation	• SmPC: Section 4.4 and Section 5.3
Missing information	
Use in patients with BMF	• None
Use in pregnant women	• SmPC: Section 4.4, Section 4.6 and Section 5.3 • Package Leaflet: Section 2
Long-term safety (>1 year)	• SmPC: Section 4.2, Section 4.4, Section 4.6, Section 4.8, and Section 5.2 • Package Leaflet: Section 4

Abbreviations: BMF, Bone marrow failure; IVH, Intravascular hemolysis; PEG, Polyethylene glycol; PNH, Paroxysmal nocturnal hemoglobinuria; SmPC, Summary of product characteristics.

V.2. Additional risk minimization measures

Guide for healthcare professionals

Objectives:

Reduce and mitigate the risks of serious infection with encapsulated bacteria, serious hypersensitivity reactions, IVH after drug discontinuation and postponement of administration, and the potential long-term effects of PEG accumulation by enhancing the awareness of the healthcare professionals regarding these potential risks, by supporting knowledge on early detection of serious infections, and by emphasizing the importance of vaccination and/or antibiotic treatment in pegcetacoplan-treated PNH patients.

Rationale for the additional risk minimization activity:

Enhance healthcare professionals' awareness on the risks of serious infection with encapsulated bacteria, serious hypersensitivity reactions, IVH after drug discontinuation and postponement of administration, and the potential long-term effects of PEG accumulation.

Target audience and planned distribution path:

The guide for healthcare professionals will be provided to all potential prescribers. It will be distributed through country-specific method directly to prescribers and provided upon request.

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

The PASS (Sobi.PEGCET-301) will be used to evaluate the effectiveness of the guide for healthcare professionals in reducing and mitigating the risk of serious infections with encapsulated bacteria. A review of individual cases will provide the incidence and reporting of serious infections with encapsulated bacteria.

Patient card

Objectives:

Reduce and mitigate the risk of serious infection with encapsulated bacteria by listing signs and symptoms of serious infections and warning to seek immediate medical attention.

Rationale for the additional risk minimization activity:

Enhance patients' awareness on the risk of serious infection with encapsulated bacteria by providing a list of signs and symptoms of serious infections.

Target audience and planned distribution path:

The patient card will be provided to all potential prescribers. It will be distributed through country-specific method directly to prescribers and provided upon request.

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

Information collected from the PASS (Study Sobi.PEGCET-301) will be used to evaluate the effectiveness of the patient card in reducing and mitigating the risk of serious infections with encapsulated bacteria. A review of individual cases will provide the incidence and reporting of serious infections with encapsulated bacteria.

Patient/carer guide

Objectives:

Reduce and mitigate the risks of serious infection with encapsulated bacteria, serious hypersensitivity reactions, and discontinuation-associated IVH by enhancing patients' awareness and knowledge on the risks and associated signs and symptoms.

Rationale for the additional risk minimization activity:

Support and educate patients on the risks associated with pegcetacoplan.

Target audience and planned distribution path:

The patient/carer guide will be provided to all patients treated with pegcetacoplan. It will be distributed through country-specific method directly to patients (e.g., via pharmacy) and provided upon request.

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

Information collected from the PASS (Study Sobi.PEGCET-301) will be used to evaluate the effectiveness of the patient/carer guide in reducing and mitigating the risk of serious infections with encapsulated bacteria. A review of individual cases will provide the incidence and reporting of serious infections with encapsulated bacteria.

Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines)

Objectives:

Reduce and mitigate the risks of serious infections with encapsulated bacteria by providing annual reminders to review mandatory revaccinations for patients in accordance with current national vaccination guidelines.

Rationale for the additional risk minimization activity:

Annual reminders will emphasize the importance of vaccination and/or antibiotic treatment in pegcetacoplan-treated PNH patients.

Target audience and planned distribution path:

Annual reminders will be sent to prescribers or pharmacists who prescribe or dispense pegcetacoplan.

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

Information collected from the PASS (Study Sobi.PEGCET-301) will be used to evaluate the effectiveness of the annual mandatory revaccination reminders in reducing and mitigating the risk of serious infections with encapsulated bacteria. A review of individual cases will provide the incidence and reporting of serious infections with encapsulated bacteria.

System for controlled distribution

Objectives:

Reduce and mitigate the risks of serious infections with encapsulated bacteria by implementation of a system for controlled distribution.

Rationale for the additional risk minimization activity:

A controlled distribution system ensures that pegcetacoplan is only dispensed after written confirmation that the patient has received vaccination against encapsulated bacteria and/or is receiving prophylactic antibiotic according to national guidelines.

Target audience and planned distribution path:

Information regarding the requirement for a controlled distribution system will be provided to all prescribers of pegcetacoplan.

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

Information collected from the PASS (Study Sobi.PEGCET-301) will be used to evaluate the effectiveness of the system for controlled distribution in reducing and mitigating the risk of serious infections with encapsulated bacteria. A review of individual cases will provide the incidence and reporting of serious infections with encapsulated bacteria.

V.3. Summary of risk minimization measures

Table 12 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important potential risks		
Serious infections	Routine risk minimization measures: • SmPC Section 4.3, Section 4.4, and Section 4.8 • Package Leaflet • Section 2, Section 3, and Section 4 Additional risk minimization measures: • Guide for healthcare professionals • Patient card • Patient/carer guide • Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines) • System for controlled distribution	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension study APL2-307 2. PASS Sobi.PEGCET-301
Serious hypersensitivity reactions	Routine risk minimization measures: • SmPC Section 4.3 and Section 4.4 • Package Leaflet Section 2 Additional risk minimization measures: • Guide for healthcare professionals • Patient/carer guide	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS Sobi.PEGCET-301

Safety concern	Risk minimization measures	Pharmacovigilance activities
IVH after drug discontinuation	Routine risk minimization measures: • SmPC Section 4.2 and Section 4.4 • Package Leaflet Section 2, Section 3, and Section 4 Additional risk minimization measures: • Guide for healthcare professionals • Patient/carer guide	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS Sobi.PEGCET-301
Immunogenicity	Routine risk minimization measures: • SmPC Section 4.8 Additional risk minimization measures: • None	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS Sobi.PEGCET-301
Malignancies and hematologic abnormalities	Routine risk minimization measures: • None. Additional risk minimization measures: • None	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS Study Sobi.PEGCET-301
Potential long-term effects of PEG accumulation	Routine risk minimization measures: • SmPC Section 4.4 and Section 5.3 Additional risk minimization measures: • Guide for healthcare professionals	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS Study Sobi.PEGCET-301
Missing information		
Use in patients with BMF	Routine risk minimization measures: • None Additional risk minimization measures: • None	Additional pharmacovigilance activities: 1. PASS Study Sobi.PEGCET-301
Use in pregnant women	Routine risk minimization measures: • SmPC Section 4.4, Section 4.6 and Section 5.3 • Package Leaflet Section 2 Additional risk minimization measures: • None	
Long-term safety (>1 year)	Routine risk minimization measures: • SmPC Section 4.2, Section 4.4, Section 4.6, Section 4.8, and Section 5.2 • Package Leaflet Section 4 Additional risk minimization measures: • None	Additional pharmacovigilance activities: 1. Collection of safety data from long-term extension Study APL2-307 2. PASS (Study Sobi.PEGCET-301)

Abbreviations: BMF, Bone marrow failure; IVH, Intravascular hemolysis; PASS, Post authorization safety study; PEG, Polyethylene glycol; SmPC, Summary of product characteristics.

Part VI: Summary of activities in the risk management plan by product

Summary of risk management plan for Aspaveli (pegcetacoplan)

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

Aspaveli's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Aspaveli should be used.

This summary of the RMP for Aspaveli 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.

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

I. The medicine and what it is used for

Aspaveli is authorized for PNH (see SmPC for the full indication). It contains pegcetacoplan as the active substance, and it is given by subcutaneous infusion.

Further information about the evaluation of Aspaveli's benefits can be found in Aspaveli's European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/aspaveli

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Aspaveli, together with measures to minimize such risks and the proposed studies for learning more about Aspaveli'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 package leaflet 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; and
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

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

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

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

If important information that may affect the safe use of Aspaveli is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks of Aspaveli are risks that need 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 Aspaveli. Potential risks are concerns for which an association with the use of this medicine is possible according to 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 (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	1. Serious infections 2. Serious hypersensitivity reactions 3. IVH after drug discontinuation 4. Immunogenicity 5. Malignancies and hematologic abnormalities 6. Potential long-term effects of PEG accumulation
Missing information	1. Use in patients with BMF 2. Use in pregnant women 3. Long-term safety (>1 year)

Abbreviation: BMF, Bone marrow failure; IVH, Intravascular hemolysis; PEG, Polyethylene glycol.

II.B. Summary of important risks

Important potential risk 1: Serious infections	
Evidence for linking the risk to the medicine	Inhibition of components of the complement system, including C3, might decrease innate immunity to encapsulated bacteria. This potentially increases the risk of serious infections from these bacteria in patients treated with pegcetacoplan. Studies have identified increased susceptibility to infection caused by encapsulated organisms as a key clinical consequence of congenital complement deficiency. Specifically, deficiency of C3 and its regulators (factor H and factor I) has been associated with severe recurrent bacterial infections caused by *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis* There have been no reports of meningococcal infections through 818.36 person-years of systemic pegcetacoplan exposure in ongoing and completed clinical trials and 626.58 person-years of systemic pegcetacoplan exposure in the post marketing setting.
Risk factors and risk groups	1. Unvaccinated patients or patients who do not maintain sufficient antibodies to the vaccines given before or during treatment might have a higher risk of infection due to encapsulated bacteria. 2. Patients with PNH-associated BMF (including aplastic anemia PNH and myelodysplastic syndrome) have a higher risk of serious infection due to neutropenia. 3. For patients who had solid organ (renal) or BMTx, receiving immunosuppressive treatment (e.g., high-dose steroids, mycophenolate mofetil, ciclosporin, and tacrolimus) is a risk factor. 4. Individuals exposed to certain bacteria through work or travel might have a higher risk of infection. Groups at risk may include day-care workers, laboratory workers, military personnel, and other individuals with heightened levels of exposure to pathogenic bacteria.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3, Section 4.4, and Section 4.8 • Package Leaflet Section 2, Section 3, and Section 4 Additional risk minimization measures: • Guide for healthcare professionals • Patient card • Patient/carer guide • Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines) • System for controlled distribution
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study names • Collection of safety data from long-term extension Study APL2-307 • PASS Sobi.PEGCET-301 See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: BMF, Bone marrow failure; BMTx, Bone marrow transplantation; PASS, Post authorization safety study; PNH, Paroxysmal nocturnal hemoglobinuria; SmPC, Summary of product characteristics.

Important potential risk 2: Serious hypersensitivity reactions	
Evidence for linking the risk to the medicine	There was 1 report of serious hypersensitivity in Study APL2-CP-PNH-204. This moderate SAE of hypersensitivity was deemed by the investigator to be related to pegcetacoplan. The event, which occurred on Day 1 (i.e., the subject's 1st day of dosing), led to the subject's discontinuation from the study. The subject was negative for anti pegcetacoplan peptide antibody response on Day 1. Another subject in Study APL2-204 had a mild TEAE of maculopapular rash deemed by the investigator to be related to pegcetacoplan. This event was temporally associated with positive serum anti-PEG antibodies but not anti pegcetacoplan peptide antibodies. The rash subsequently resolved, and anti-PEG serology became negative despite uninterrupted treatment with pegcetacoplan. These 2 cases of hypersensitivity were treated and resolved. In Study APL2-302, 18 subjects treated with pegcetacoplan experienced a hypersensitivity event. Most were mild or moderate in intensity. Erythema, rhinitis allergic, and acute respiratory failure were the most common TEAEs. 5 subjects experienced hypersensitivity events that were considered related to pegcetacoplan (acute respiratory failure, erythema, hypersensitivity pneumonia, mechanical urticaria, and pruritus). 3 subjects had severe hypersensitivity events, including 1 subject who had an SAE of hypersensitivity pneumonitis that led to study discontinuation. In Study APL2-308, 12 subjects treated with pegcetacoplan experienced a hypersensitivity event. All were mild or moderate in intensity. Erythema, rash, and rash maculopapular were the most common TEAEs. 3 subjects experienced hypersensitivity events that were considered related to pegcetacoplan (rash [2 events] and rash maculopapular). In Study APL2-302, ISRs were frequently reported, although none was severe or serious, and treatment continued in all subjects without sequelae. In Study APL2-308, 16 subjects in the overall pegcetacoplan group had at least 1 ISR. All ISRs were mild in severity; there were no moderate or severe ISRs. Erythema was the most commonly reported ISR. The risk of serious hypersensitivity reactions is a theoretical potential risk because of the mechanism of action of pegcetacoplan and reports on potential for immunogenicity from PEG. In the post marketing setting, very limited information was provided for 2 cases of anaphylactic reaction in subject on pegcetacoplan; however, in both cases, pegcetacoplan treatment was continued, and the events resolved. In addition, 1 case of supposed anaphylactic shock has been reported, which was considered by the company to be related to pegcetacoplan given the plausible temporal relationship and lack of alternate etiologies.
Risk factors and risk groups	Patients with a history of hypersensitivity to PEG are considered to have an increased risk of being hypersensitive to pegcetacoplan. In the pegcetacoplan clinical development program, the immunogenicity potential of pegcetacoplan was assessed by evaluation of samples using validated assays for assessment of anti-pegcetacoplan peptide antibody and anti-PEG antibody in human serum samples. There was no apparent correlation of antibody development to an altered PK profile. There has been no observed correlation of ADA development to clinical response or AEs in healthy subjects or subjects with PNH.

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 and Section 4.4 • Package Leaflet Section 2 Additional risk minimization measures: • Guide for healthcare professionals • Patient/carer guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Collection of safety data from long-term extension Study APL2-307 • PASS Sobi.PEGCET-301 See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: ADA, Antidrug antibodies; ISR, Injection site reaction; PASS, Post authorization safety study; PEG, Polyethylene glycol; PK, pharmacokinetic; PNH, Paroxysmal nocturnal hemoglobinuria; SAE, Serious adverse event; SmPC, Summary of product characteristics; TEAE, Treatment-emergent adverse event.

Important potential risk 3: IVH after drug discontinuation	
Evidence for linking the risk to the medicine	The PNH disease process and mechanism of control for it by complement inhibition is the source of this risk. Inhibition of complement C3 protects circulating RBCs, produced by mutant stem cell clones, from hemolysis. Discontinuation of treatment risks acute hemolytic crisis because of these RBCs becoming vulnerable to destruction in patients with PNH. Hemolysis occurring in study subjects after sudden pegcetacoplan withdrawal has been observed. In Study APL2-204, 1 subject had pegcetacoplan administration withheld for 8 days because of a herpes zoster infection. The subject was instructed by the investigator to resume administration immediately and received pegcetacoplan on the next 2 days. On the following day, the subject withheld pegcetacoplan dosing because of abdominal discomfort and was subsequently diagnosed with severe hemolysis. The gap in this subject's pegcetacoplan dosing was associated with the onset of hemolysis. In Study APL2 CP0514, pegcetacoplan treatment was temporarily ceased for 1 subject following an SAE of alanine aminotransferase increased. 20 days later, the subject had an SAE of anemia that was attributed to rebound hemolysis following cessation of pegcetacoplan treatment. In the RCP of Study APL2-302, some hemolytic events occurred in the eculizumab group for which the investigator assessed the causal relationship to the study drug as possibly or definitely related to pegcetacoplan. It should be noted that subjects were not receiving pegcetacoplan during the RCP, but the investigator attributed the event to the discontinuation of pegcetacoplan after the run-in period. No events of hemolysis occurred because of missed or delayed pegcetacoplan or eculizumab doses. In Study APL2-302, 22 subjects treated with pegcetacoplan experienced a hemolytic event. Most events were moderate or severe in intensity. 8 subjects experienced serious hemolytic events. Hemolysis was the most common TEAE occurring in 19 subjects (23.8 %). 3 subjects experienced hemolysis that were considered related to pegcetacoplan. As a result of the hemolytic events, the dose of pegcetacoplan was increased in 10 subjects, and the study drug was withdrawn in 5 subjects. In the randomized controlled period of the study, hemolysis TEAE occurred less frequently

	in the pegcetacoplan group than in the eculizumab group. This suggests that no additional risk for hemolysis is associated with pegcetacoplan treatment. In Study APL2-308, 2 subjects treated with pegcetacoplan experienced a hemolytic event. 1 event was moderate and 1 event was severe in intensity. 1 additional subject in the standard of care to pegcetacoplan group experienced a moderate event of hemolysis. In all 3 instances, the events resulted in a dose increase. In the post marketing setting, there has been one report of hemolysis that occurred after pegcetacoplan discontinuation. Symptoms resolved in 1 to 2 days after treatment with pegcetacoplan was resumed.
Risk factors and risk groups	Patients with PNH who are being treated with a complement inhibitor and who have not been established on an effective alternative therapy at the time of discontinuation of a complement inhibitor are at higher risk for IVH after drug discontinuation.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 and Section 4.4 • Package Leaflet Section 2, Section 3, and Section 4 Additional risk minimization measures: • Guide for healthcare professionals • Patient/carer guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study names • Collection of safety data from long-term extension Study APL2-307 • PASS Sobi.PEGCET-301 See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: IVH, Intravascular hemolysis; PNH, Paroxysmal nocturnal hemoglobinuria; RBC, Red blood cell; SmPC, Summary of product characteristics; TEAE, Treatment-emergent adverse event.

Important potential risk 4: Immunogenicity	
Evidence for linking the risk to the medicine	Immunogenicity is a known potential of all medicinal products and is a class effect of all therapeutic peptides and proteins. No significant data have been identified for risk factors for immunogenicity in patients with PNH, neither within the conducted clinical trials for PNH nor identified in further publicly available articles or literature related to immunogenicity or antibodies to drug.
Risk factors and risk groups	In the pegcetacoplan clinical development program, the immunogenicity potential of pegcetacoplan was assessed by evaluation of samples using validated assays for assessment of anti pegcetacoplan peptide antibody and anti-PEG antibody in human serum samples. There was no apparent correlation of antibody development to an altered PK profile. There has been no observed correlation of ADA development to clinical response or AEs in healthy subjects or subjects with PNH.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 Additional risk minimization measures: • None

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Collection of safety data from long-term extension Study APL2-307 • PASS (Sobi.PEGCET-301) See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: AE, Adverse event; ADA, Antidrug antibodies; PASS, Post authorization safety study; PEG, Polyethylene glycol; PK, pharmacokinetic; PNH, Paroxysmal nocturnal hemoglobinuria; SmPC, Summary of product characteristics.

Important potential risk 5: Malignancies and hematologic abnormalities	
Evidence for linking the risk to the medicine	Prior experience of PNH patients treated with C5 inhibitors and review of published data describing the risk of malignancies and hematologic abnormalities in patients with congenital complement deficiencies is the main reason for including this as an important potential risk.
Risk factors and risk groups	None identified.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Collection of safety data from long-term extension Study APL2-307 • PASS (Sobi.PEGCET-301) See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: PASS, Post authorization safety study; PNH, Paroxysmal nocturnal hemoglobinuria.

Important potential risk 6: Potential long-term effects of PEG accumulation	
Evidence for linking the risk to the medicine	Preclinical findings from nonclinical studies of pegcetacoplan in rabbits and monkeys are the main reasons for including this as an important potential risk. In general, PEG-associated cytoplasmic vacuolation has been considered an adaptive tissue response to long-chain PEG, which is widely considered a non-adverse finding, if not accompanied by evidence of cellular distortion, necrosis, degeneration, inflammation, or disturbed body function. The only exception is represented by the kidney, in which epithelial degeneration was observed. Short-term safety of PEG has been studied extensively without identification of toxicity beyond reports of renal tubular cell vacuolation and degeneration at very high-dose levels. In some instances, vacuolation was significant, thus leading to tissue distortion, but yet without demonstrated adverse functional outcomes.
Risk factors and risk groups	None identified.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 and Section 5.3 Additional risk minimization measures: • Guide for healthcare professionals

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Collection of safety data from long-term extension Study APL2-307 • PASS (Sobi.PEGCET-301) See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: PASS, Post authorization safety study; PEG, Polyethylene glycol; SmPC, Summary of product characteristics.

Important missing information 1: Use in patients with BMF	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS (Sobi.PEGCET-301) See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: BMF, Bone marrow failure; PASS, Post authorization safety study.

Important missing information 2: Use in pregnant women	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, Section 4.6 and Section 5.3 • Package Leaflet Section 2 • Additional risk minimization measures: • None

Abbreviations: SmPC, Summary of product characteristics.

Important missing information 3: Long-term safety (>1 year)	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, Section 4.4, Section 4.6, Section 4.8, Section 5.2 • Package Leaflet Section 4 Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Collection of safety data from long-term extension Study APL2-307 • PASS (Sobi.PEGCET-301) See Section II.C of this summary for an overview of the post authorization development plan.

Abbreviations: PASS, Post authorization safety study; SmPC, Summary of product characteristics.

II.C Post authorization 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 Aspaveli.

II.C.2 Other studies in post authorization development plan

PASS of pegcetacoplan in patients with PNH (Study Sobi.PEGCET-301)

This is a multinational, multicenter, observational PASS to assess the long-term safety of pegcetacoplan in a real-world setting. The purpose of this study is to gain more data on the long-term safety profile of pegcetacoplan and evaluate if the use of pegcetacoplan in adult patients with PNH increases the risk of certain adverse outcomes. The primary objective of this study is to evaluate the occurrence of serious infections in patients with PNH treated with pegcetacoplan. Patient data in this study will be extracted from the database of the ongoing observational study Sobi.PEGCET-304 which is collecting all AEs. This study is observational and will not affect the patient and investigator relationship, nor influence the investigator's drug prescription or therapeutic management of the patient. The decision to treat patients with pegcetacoplan will be independent from the decision to enroll patients in the study.

An open-label, nonrandomized, multicenter extension study to evaluate the long-term safety and efficacy of pegcetacoplan in the treatment of PNH (Study APL2-307)

An open-label, nonrandomized, multicenter extension phase 3 long-term extension study for patients with PNH. This extension study protocol was developed to continue evaluation of the long-term safety and efficacy of pegcetacoplan in subjects with PNH. The objectives of this study are to establish the long-term safety of pegcetacoplan in subjects with PNH and to establish the long-term efficacy of pegcetacoplan in subjects with PNH. Subjects who have completed other pegcetacoplan PNH clinical trials are eligible to participate in this trial.

Part VII: Annexes

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Annex 4 Specific adverse drug reaction follow-up forms

N/A

Annex 6 Details of proposed additional risk minimization activities (if applicable)

Key messages of the additional risk minimization measures

Prior to the launch of Aspaveli in each Member State, the MAH must agree about the content and format of the educational and controlled distribution program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The educational and controlled distribution program is aimed at:

- Ensuring patients receive vaccinations against *N. meningitidis, S. pneumoniae,* and *H. influenzae* at least 2 weeks before starting treatment with Aspaveli.
- Ensuring that patients who cannot wait 2 weeks before starting treatment with Aspaveli receive broad-spectrum antibiotics until 2 weeks after receiving the vaccines.
- Ensuring that Aspaveli is only dispensed after written confirmation that the patient has received vaccination against *N. meningitidis, S. pneumoniae*, and *H. influenzae* and/or is receiving prophylactic antibiotic according to national guidelines.
- Ensuring prescribers or pharmacists receive annual reminders of mandatory revaccinations in accordance with current national vaccination guidelines (including *N. meningitidis, S. pneumoniae*, and *H. influenzae*).
- Providing information about the signs and symptoms of serious infections to healthcare providers and patients.
- Ensuring that prescribers provide patients with the package leaflet and patient card and explain the main risks of Aspaveli using these materials.
- Ensuring that patients who experience symptoms of serious infections seek emergency medical treatment and present their patient card to the emergency care provider.
- Educate prescribers and patients about the risk of IVH after discontinuation of the medicinal product and postponement of administration and the need to maintain effective complement inhibitor treatment.
- Educate prescribers about the risk of potential long-term effects of PEG accumulation and the recommendation to monitor as clinically indicated, including through laboratory testing.

The MAH shall ensure that in each Member State where Aspaveli is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Aspaveli have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

1. The SmPC
2. Guide for healthcare professionals
3. Patient card
   - **Guide for healthcare professionals:**
     - Treatment with Aspaveli may increase the risk of serious infections with encapsulated bacteria.
     - The need for patients to be vaccinated against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or receive antibiotic prophylaxis.
     - Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines).
     - Risk of IVH after discontinuation and postponement of administration of the medicinal product, its criteria, the required posttreatment monitoring, and its proposed management.
     - Risk of potential long-term effects of PEG accumulation and the recommendation to monitor as clinically indicated, including through laboratory testing.
     - The need to educate patients/carers of the following:
       - The risks of treatment with Aspaveli
       - Signs and symptoms of serious infections, hypersensitivity reactions, and what action to take
       - The patient/carer guides and its content
       - The need to carry the patient card and to tell any healthcare practitioner that he/she is receiving treatment with Aspaveli
       - The requirement for vaccinations/antibiotic prophylaxis
       - Enrollment in PASS (where available)
     - Instructions on how to handle possible AEs.
     - Information about PASS (where available), the importance of contributing to such a study, and how to enter patients.
     - Remarks on the importance of reporting on specific adverse reactions, namely: serious infections, serious hypersensitivity reactions, and risk of IVH after discontinuation of the medicinal product.
   - **Patient card:**
     - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Aspaveli.
     - Signs or symptoms of the serious infections and warning to seek immediate attention from a healthcare professional if above is present.
     - Contact details of the Aspaveli prescriber.

The patient information pack:

1. Patient information leaflet
2. Patient/carer guide
    - **Patient/carer guide:**
        - Treatment with Aspaveli may increase the risk of serious infections with encapsulated bacteria, serious hypersensitivity reactions, and risk of IVH after discontinuation of the medicinal product.
        - A description of the signs and symptoms of serious infections, hypersensitivity reactions, IVH after discontinuation of the medicinal product, and the need to seek emergency care at the nearest hospital.
        - The importance of vaccination prior to treatment with Aspaveli and/or to receive antibiotic prophylaxis.
        - Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines).
        - Detailed description of the modalities used for the self-administration of Aspaveli.
        - Recommendation for use of effective contraception in women of childbearing potential.
        - Remarks on the importance of reporting on specific adverse reactions, namely: serious infections, serious hypersensitivity reactions, and risk of IVH after discontinuation of the medicinal product.
        - Instructions on how to view the patient self-treatment video on any internet-connected device.
        - Enrollment in PASS (where available).

Annual reminder of mandatory revaccinations

The MAH shall send a reminder annually to prescribers or pharmacists who prescribe/dispense Aspaveli in order that the prescriber/pharmacist checks if a revaccination against *N. meningitidis, S. pneumoniae,* and *H. influenzae* is required for his/her patients on treatment with Aspaveli, in accordance with national vaccination guidelines.

System for controlled distribution

The MAH shall ensure that in each Member State where Aspaveli is marketed, a system aimed to control distribution beyond the level of routine risk minimization measures is in place. The following requirement needs to be fulfilled before the product is dispensed.

- Submission of written confirmation, or equivalent as permitted by national legislation, of the patient's vaccination against *N. meningitidis, S. pneumoniae,* and *H. influenzae* and/or prophylactic antibiotic treatment according to national vaccination guidelines.