

**A single arm, multicenter observational study to evaluate effectiveness of pegcetacoplan under real world conditions in patients with paroxysmal nocturnal hemoglobinuria (PNH)**

Protocol Number: **Sobi.PEGCET-304**

Short title: **COMPLETE**

Type of Study: **Non-Interventional Study**

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## Synopsis

STUDY IDENTIFIERS	
Title of study	A single arm, multicenter observational study to evaluate effectiveness of pegcetacoplan under real world conditions in patients with paroxysmal nocturnal hemoglobinuria (PNH)
Clinical study number	Sobi.PEGCET-304 (COMPLETE)
Type of study	Observational study
STUDY OBJECTIVES	
Primary objective	To describe the effectiveness of pegcetacoplan in the treatment of adult patients with PNH under real world conditions
Secondary objectives	<ul style="list-style-type: none"><li>• To describe quality of life (QoL) in patients with PNH treated with pegcetacoplan</li><li>• To describe health care resource use in patients with PNH treated with pegcetacoplan</li><li>• To describe physician and patient satisfaction with pegcetacoplan treatment</li></ul>
STUDY ENDPOINTS	
Primary endpoint	<ul style="list-style-type: none"><li>• Change in observed hemoglobin level from initiation of treatment with pegcetacoplan to 6 months</li></ul>

Secondary endpoints	<p>Secondary endpoints supporting the primary objective:</p> <ul style="list-style-type: none"> <li>• Change in laboratory values from initiation of pegcetacoplan treatment to 6 months <ul style="list-style-type: none"> <li>○ Lactate Dehydrogenase (LDH)</li> <li>○ Absolute Reticulocyte Count (ARC)</li> <li>○ Indirect/ total bilirubin</li> <li>○ Haptoglobin</li> <li>○ Ferritin</li> </ul> </li> <li>• Laboratory values at initiation of pegcetacoplan treatment and each 6 months until end of study <ul style="list-style-type: none"> <li>○ Hemoglobin (Hb)</li> <li>○ Lactate Dehydrogenase (LDH)</li> <li>○ Absolute Reticulocyte Count (ARC)</li> <li>○ Indirect/ total bilirubin</li> <li>○ Haptoglobin</li> <li>○ Ferritin</li> </ul> </li> <li>• At initiation of pegcetacoplan treatment and each 6 months until end of study <ul style="list-style-type: none"> <li>○ Hemoglobin (Hb) <math>\geq 12</math> g/dL</li> <li>○ Increase in hemoglobin (Hb) levels of <math>\geq 2</math> g/dL</li> <li>○ Acute hemolytic event requiring additional intervention</li> </ul> </li> <li>• Annualized number of red blood cell transfusions and units during pegcetacoplan treatment until end of study compared to the 12-month period before pegcetacoplan treatment</li> </ul> <p>Secondary endpoints:</p> <ul style="list-style-type: none"> <li>• Patient reported outcome (PRO) scale scores (FACIT-Fatigue, QLQ AA/PNH) at initiation of treatment with pegcetacoplan and every 6 months until end of study</li> <li>• Health care resource use: Annualized number of hospitalizations and emergency room visits during pegcetacoplan treatment until end of study compared to the 12-month period before pegcetacoplan treatment</li> <li>• Patient treatment satisfaction (5-point scale) every 6 months until end of study</li> <li>• Physician treatment satisfaction (5-point scale) every 6 months until end of study</li> </ul>
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**BACKGROUND****Background and rationale**

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired chronic clonal disorder of hematopoietic and mature blood cells. It is characterized by debilitating complement-mediated hemolytic anemia, as well as bone marrow failure, an increased risk of thrombosis and a need for red blood cell (RBC) transfusions.

Although C5 inhibition controls intravascular hemolysis (IVH) in untreated PNH it cannot address extravascular hemolysis (EVH). Ongoing anemia related to C3-mediated EVH and residual IVH is observed in up to 88% of C5-inhibitor treated patients, which contributes to transfusion dependence in up to 52% of these patients.

Pegcetacoplan is a C3 complement inhibitor which exerts a broad regulation of the complement cascade by acting proximal to both C3b and the Membrane Attack Complex (MAC) formation, thereby controlling the mechanisms that lead to extravascular as well as intravascular hemolysis.

As pegcetacoplan is a new product on the market, with a new mechanism of action, there is an urgent need to provide data to treaters, payers and the PNH community on the real-world usage and effectiveness of pegcetacoplan. This study aims to fill part of that knowledge gap and to add to the knowledge base regarding the use of pegcetacoplan in routine medical practice. Another important rationale for this study is to provide information on pre and post pegcetacoplan treatment outcomes.



<b>STUDY DESIGN AND METHODS</b>	
Study design	<p>This is a 24-month multicenter, observational study designed to describe the real world effectiveness of pegcetacoplan in patients with PNH. Patients meeting the eligibility criteria will be enrolled in the study at the enrollment visit and followed prospectively for 24 (+/- 3) months. The scope of the study is to collect both retrospective and prospective data. The main part of the study will be prospective, collecting data on effectiveness, safety, patient- and clinician-reported outcomes and health care resource use. Routine treatment data will be collected for 12 months prior to pegcetacoplan treatment start which will consist of information on PNH treatment, blood transfusions and healthcare resource use. Routine pegcetacoplan data may be collected from the date pegcetacoplan was first approved in the respective country participating in the study. This means that the data collection period will vary depending on when pegcetacoplan was prescribed. Due to the observational nature of the study the protocol does not dictate any visit schedule and the patients visit their treating physician as per clinical routine.</p>
Number of patients planned	<p>All centers in selected countries managing PNH patients treated with pegcetacoplan will be invited to participate in this observational study. The study plans to include approximately 200 patients at 80 sites in Europe, Middle East, Canada and Australia.</p>
Diagnosis and main criteria for inclusion	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> <li>1. Patients <math>\geq 18</math> years of age with a documented PNH diagnosis.</li> <li>2. Patient started routine treatment with pegcetacoplan for PNH before enrollment or prescribed pegcetacoplan at enrollment. Decision to initiate treatment shall be made by the treating physician and independently from the decision to include the patient in the study.</li> <li>3. Patient is willing and able to provide written informed consent to participate in the study in a manner approved by the Independent Ethics Committee/ Research Ethics Board and local regulations.</li> </ol> <p>Exclusion criteria:</p> <ol style="list-style-type: none"> <li>1. Enrollment in a concurrent clinical interventional study, or intake of an Investigational Medicinal Product (IMP), within three months prior to the start of the current pegcetacoplan treatment.</li> <li>2. Initiated current treatment with pegcetacoplan in an interventional study.</li> </ol>

Medicinal product	Patients will be prescribed pegcetacoplan, according to clinical practice and investigator's judgement. The choice of treatment will not be dictated by the study protocol.
Sample size	With a sample size of 200 patients and assuming a standard deviation of 4 g/dL Hb for the change in the primary endpoint, the mean change from baseline will be estimated with a level of accuracy of 0.55 g/dL which would give a sufficient precision for an expected mean change in primary endpoint from baseline of 2-3 g/dL (2.4 g/dL at week 16 in PEGASUS) by keeping the lower limit of the 95% confidence interval above zero. In addition, a sample size of 200 patients would compensate for dropouts during the study while maintaining the lower limit above zero as well as allowing for subgroup analyses.
Statistical methods	No formal hypothesis testing will be performed for the primary or secondary endpoints. The change in observed Hb levels will be presented by descriptive statistics for patients treated with pegcetacoplan for at least 6 months. In addition, the estimated mean change from baseline together with the corresponding 95% confidence interval will also be presented. Pre- and post-analysis, before and after switch to pegcetacoplan, will be described. Continuous variables will be characterized with non-missing observations, mean and standard deviation, median and interquartile range, minimum and maximum, and number of missing data. Categorical variables will be characterized by the frequency and percent distribution in each category for non-missing data and missing data, as appropriate.
Milestones	First patient enrolled in the observational study is expected Q3 2023. Last patient enrolled is expected Q3 2025. Last patient out is expected Q3 2027. Final report Q1 2028

# 1 Abbreviations and definition of terms

## 1.1 List of Abbreviations

Term	Definition
AE	Adverse event
AH50	Alternative complement function test
C3	Complement 3 protein
CI	Confidence interval
CH50	Classical complement function test
CRO	Contract research organization
CRF	Case report form
CSR	Clinical study report
eCRF	Electronic case report form
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EU	European Union
EEA	European economic area
EVH	Extravascular hemolysis
FACIT	Functional assessment of chronic illness therapy
FDA	U.S. Food and Drug Administration
GCP	Good clinical practice
GDPR	General data protection regulation
GPP	Good pharmacoepidemiology practice
GVP	Good pharmacovigilance practice
Hb	Hemoglobin
HCP	Health care professional
HSCT	Hematopoietic stem cell transplantation
HRQoL	Health related quality of life
ICF	Informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IEC/REB	Independent ethics committee/Research ethics board
IVH	Intravascular hemolysis
ISPE	Society of Pharmacoepidemiology
MAC	Membrane attack complex
PK	Pharmacokinetics
PD	Pharmacodynamics
PNH	Paroxysmal nocturnal hemoglobinuria
PRO	Patient reported outcome
RBC	Red blood cell
QLQ-AA/PNH	Quality of life questionnaire for patients with aplastic anemia and/or paroxysmal nocturnal hemoglobinuria
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
Sobi	Swedish Orphan Biovitrum AB (publ)

## 1.2 List of Definitions

Concomitant PNH medication	Medication specifically given for the treatment of PNH, such as anticoagulants, erythropoiesis stimulating agents, corticosteroids other immunosuppressive therapies, thrombopoietin receptor agonists, iron chelators.
Not related AE	The AE does not follow a reasonable temporal sequence from pegcetacoplan administration or can be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).
Related AE	The AE follows a reasonable temporal sequence from the pegcetacoplan administration and cannot be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications).
Routine visit	Any visit (i.e., on-site visit, home visit, or phone call) performed for clinical need/assessment. The definition does not include visits performed exclusively for laboratory tests.

## **2 Ethics**

### **2.1 Independent ethics committee or research ethics board**

It is the responsibility of the investigator to obtain approval of the study protocol, potential amendments and the written patient information and ICF from the IEC/REB. The investigator should file all correspondence with the IEC/REB. Copies of IEC/REB correspondence and approvals should be forwarded to the CRO.

### **2.2 Patient information and consent**

It is the responsibility of the investigator to ensure that each patient, prior to any study-related activities, obtains full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. This can be done at a routine clinic visit, a home visit or during a routine phone call with the patient if allowed by local regulations. The patients must be informed about their right to withdraw from the study at any time without having to provide a reason for their withdrawal.

The written patient information and/or ICF must not be changed without prior approval from Sobi. Before any revisions are implemented, the revised written patient information and/or ICF must also be approved by the IEC/REB.

It is the responsibility of the investigator or designee to obtain signed informed consent (or witnessed verbal consent according to applicable regulations) from all patients prior to any study-related activities. The patients should receive a copy of the written information and the signed ICF. The patient should have sufficient time to consider their study participation before providing their consent.

If a female study participant or a female partner of a male participant becomes pregnant during the study period, a separate consent form should be collected before collecting any details on the pregnancy, its outcome and the birth and health of the baby in accordance with local regulations.

## **3 Background**

PNH is a rare acquired chronic clonal disorder of hematopoietic and mature blood cells. It is characterized by debilitating complement-mediated hemolytic anemia, as well as bone marrow failure, an increased risk of thrombosis and a need for RBC transfusions. If not adequately managed, it may have a significant impact on morbidity and mortality [1, 2, 3].

Evidence of the prevalence of PNH in Europe is very limited. However, using a conservative approach with a wide definition of PNH, the prevalence is estimated to be around 0.4/10,000 persons [3, 6, 7].

The course of the disease before the advent of complement inhibitors was investigated by Hillmen and colleagues who studied a group of 80 consecutive patients with PNH who were

referred to Hammersmith Hospital, London, between 1940 and 1970 [1]. The patients had been followed-up long-term, up to 48 years after diagnosis. The median actuarial survival was 10 years, with 28% of the patients surviving for 25 years. Death was directly attributable to PNH or to bone marrow hypoplasia in 58% of the patients who died. At least 39% of the patients had venous thrombosis at some time during their illness. Many patients had initial thromboses that were life-threatening [1].

The development of targeted terminal complement C5 inhibitors, such as eculizumab and ravulizumab, transformed outcomes for patients with PNH by controlling IVH. C5 inhibitors prevent terminal complement mediated platelet and white-cell activation and destruction, thereby leading to a marked reduction in thrombosis, which is the main life-threatening complication of PNH. C5 inhibition also ameliorates anemia and reduces the need for transfusions and prevents many PNH complications such as kidney failure and pulmonary hypertension [8].

Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for PNH, but it is associated with high morbidity and mortality. Therefore, in the era of therapeutic complement inhibition, the role of HSCT seems restricted to a few rare indications for PNH patients [11].

Although C5 inhibition controls (IVH) in untreated PNH it cannot address extravascular hemolysis (EVH). Thus, although eculizumab and ravulizumab are effective in preventing C5-dependent IVH mediated by the MAC, surviving PNH erythrocytes become opsonized with C3 fragments and are removed by extravascular hemolysis in the liver and spleen. EVH is observed in most patients with PNH who are being treated with C5 inhibitors and leads to reduced erythrocyte half-life (10 to 13 days). EVH can manifest as persistent anemia despite C5 inhibitor treatment and may contribute to the need for continued blood transfusions [8].

Ongoing anemia related to C3-mediated EVH and residual IVH is observed in up to 88% of C5-inhibitor treated patients, which contributes to transfusion dependence in up to 52% of these patients [12].

Pegcetacoplan is a C3 inhibitor that 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. Pegcetacoplan exerts a broad regulation of the complement cascade by acting proximal to both C3b and the MAC formation, thereby controlling the mechanisms that lead to extravascular as well as intravascular hemolysis.

Pegcetacoplan has undergone a full clinical development program from phase 1-3. The phase 1b study PADDOCK (APL2--CP-PNH-204) evaluated safety, tolerability, PK, and PD in 23 complement inhibitor naïve PNH patients, and the phase 2a study PALOMINO (APL2-202) evaluated safety, tolerability, PK, PD, and efficacy in 4 eculizumab naïve patients for up to one year.

The phase 3 PEGASUS trial (APL2-302) showed that in patients with persistent anemia despite the C5 inhibitor eculizumab therapy, the C3 inhibitor pegcetacoplan was superior to eculizumab with respect to the change in Hb levels from baseline and provided improvements in key hematologic and clinical variables, such as freedom from transfusion. Pegcetacoplan demonstrated head-to-head superiority in adjusted least square (LS) mean change in Hb levels

(3.84 g/dL increase; 95% CI 2.33-5.34) versus eculizumab, resulting in transfusion avoidance (pegcetacoplan: 85.4%; eculizumab: 15.4%). These benefits were observed regardless of baseline transfusion requirement.

In addition to improvements in hematologic variables, pegcetacoplan also demonstrated clinically meaningful improvements in HRQoL (FACIT-Fatigue, EORTC QLQ-C30 and Linear Analog Scale Assessment (LASA)) [13]. Pegcetacoplan was also well tolerated with an acceptable safety profile [8, 9].

The phase 3 study PRINCE (APL2-308) evaluated efficacy, safety and tolerability in PNH patients with no complement inhibitor treatment  $\geq 3$  months prior to study entry. The study showed that pegcetacoplan was effective and demonstrated a favorable safety profile in complement-inhibitor naïve patients and provided rapid and sustained Hb stabilization and rapid control of IVH as seen by substantial improvements in LDH levels [10].

Patients from previous clinical development studies are enrolled in a long-term extension study (APL-307), which evaluates the longer-term safety and efficacy of pegcetacoplan over an additional four-year period. APL-307 includes a substudy to evaluate the management of acute hemolytic events with acute adjustments in pegcetacoplan dosing.

Pegcetacoplan was approved by FDA on 14 May 2021 under the trade name Empaveli “for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)”, and by EMA on 15 December 2021 under the trade name Aspaveli “indicated in the treatment of adult patients with PNH who are anaemic after treatment with a C5 inhibitor for at least 3 months.”

### **3.1 Study rationale**

The efficacy and safety of pegcetacoplan has been assessed under clinical trial conditions from relatively short treatment duration and limited number of patients given the rareness of the disease. Clinical trials also have limitations such as mandated dose and treatment interval, restrictions in the population studied and/or the duration of the treatment.

As pegcetacoplan is a new product on the market, with a new mechanism of action, there is an urgent need to provide data to treaters, payers and the PNH community on the real-world usage and effectiveness of pegcetacoplan. This study aims to fill part of that knowledge gap and to add to the knowledge base regarding the use of pegcetacoplan in routine medical practice. Another important rationale for this study is to provide information on pre and post pegcetacoplan treatment outcomes.

### **3.2 Potential risks and benefits**

This is an observational study and is therefore not linked to any medical risks for the patients. Assessments are conducted in accordance with each site’s clinical practice and are therefore not considered to pose any additional burden on the patients.



PRO questionnaires will be provided to the patients but due to the observational nature of the study, they are not mandatory to complete. No risks related to completing PROs have been identified.

Data confidentiality risks (e.g., the possibility of identifying the person concerned) exist whenever data is collected, stored, used and transmitted. These risks cannot be completely ruled out although the Sponsor has measures in place to ensure data protection. See section 3.2.1 below.

As this is an observational study, participation is not expected to have any particular benefit for the enrolled patients. The results from the study may help in improving knowledge on treatment with pegcetacoplan in patients with PNH in the future.

### **3.2.1 Confidentiality of personal data**

The following risk mitigations are in place to maintain confidentiality of personal data collected within the study.

Personal data collected and processed in the study will be coded. The coded personal data can only be directly traced back to a specific patient by using the code key. The code key will never leave the study site and only authorized personnel will have access to it.

Any reports, publications or presentations resulting from the study will never contain personal data that directly identifies a patient.

As the Sponsor of the study is located within the European Union personal data will be handled in accordance with the European data protection regulation, GDPR [14]. When coded personal data are transferred to, or processed in countries outside the EU/EEA, where the laws may not protect personal data to the same extent as the laws in the EU/EEA, Sobi is responsible to take all reasonable steps to ensure that the level of protection and confidentiality of personal data is the same as required in the EU/EEA.

## **4 Study objectives and endpoints**

### **4.1 Primary objective**

To describe the effectiveness of pegcetacoplan in the treatment of adult patients with PNH under real world conditions.

#### **4.1.1 Primary endpoint**

Change in observed hemoglobin level from initiation of treatment with pegcetacoplan to 6 months.

### 4.1.2 Secondary endpoints supporting the primary objective

- Change in laboratory values from initiation of pegcetacoplan treatment to 6 months
  - Lactate Dehydrogenase (LDH)
  - Absolute Reticulocyte Count (ARC)
  - Indirect/ total bilirubin
  - Haptoglobin
  - Ferritin
- Laboratory values at initiation of pegcetacoplan treatment and each 6 months until end of study
  - Hemoglobin (Hb)
  - Lactate Dehydrogenase (LDH)
  - Absolute Reticulocyte Count (ARC)
  - Indirect/ total bilirubin
  - Haptoglobin
  - Ferritin
- At initiation of pegcetacoplan treatment and each 6 months until end of study
  - Hemoglobin (Hb)  $\geq 12$  g/dL
  - Increase in hemoglobin (Hb) levels of  $\geq 2$  g/dL
  - Acute hemolytic event requiring additional intervention
- Annualized number of red blood cell (RBC) transfusions and units during pegcetacoplan treatment until end of study compared to the 12-month period before pegcetacoplan treatment

## 4.2 Secondary objectives

- To describe QoL in patients with PNH treated with pegcetacoplan
- To describe health care resource use in patients with PNH treated with pegcetacoplan.
- To describe physician and patient satisfaction with pegcetacoplan treatment

### 4.2.1 Secondary endpoints

- PRO scale scores (FACIT-Fatigue and QLQ AA/PNH) at initiation of treatment with pegcetacoplan and every 6 months until end of study

- Health care resource use: Annualized number of hospitalizations and emergency room visits during pegcetacoplan treatment until end of study compared to the 12-month period before pegcetacoplan treatment.
- Patient treatment satisfaction (5-point scale) every 6 months until end of study
- Physician treatment satisfaction (5-point scale) every 6 months until end of study

## 5 Study conduct

### 5.1 Milestones

The study will start in a country once pegcetacoplan is available and patients are treated according to clinical practice. First global patient in is expected in Q3 2023. It is estimated that the last patient will be enrolled approximately 24 months after first patient in (2-year enrollment period).

Milestone	Timeline*
First patient in	Q3 2023
Last patient in/end of enrollment period	Q3 2025
Last patient out	Q3 2027
Final study report	Q1 2028

*\*Timelines are subject to change, updates to planned milestones will not constitute a reason for amending the protocol but will be tracked separately until the protocol is amended for any other reason*

### 5.2 Overall study design and plan

This is a 24-month multicenter observational study designed to describe the real-world effectiveness of pegcetacoplan in patients with PNH.

The study plans to include approximately 200 patients at 80 sites in Europe, Middle East, Canada and Australia. To participate in the study a patient should be diagnosed with PNH and treated with pegcetacoplan as part of their routine medical care. The choice of treatment is not dictated by the study protocol.

All eligible patients at the study sites will be invited to participate in the study during a routine visit.

Patients meeting the eligibility criteria will be enrolled in the study at the enrollment visit and followed prospectively for 24 (+/- 3) months. Patients will come to their routine visits and the available data (as described in this protocol) from each visit will be collected for study purposes.

The scope of the study is to collect both retrospective and prospective data. The main part of the study will be prospective, collecting data on effectiveness, safety, patient- and clinician-reported outcomes and health care resource use. Routine treatment data will be collected for 12 months prior to pegcetacoplan treatment start which will consist of information on PNH treatment, blood transfusions and healthcare resource use. Routine pegcetacoplan data may be collected from the date pegcetacoplan was first approved in the respective country participating in the study. This means that the data collection period will vary depending on when pegcetacoplan was prescribed. The retrospective data will be based on the information available in the patient's medical records.

Due to the observational nature of the study, the protocol does not dictate any visit schedule and the patients visit their treating physician as per clinical routine. This means that the number of visits during the prospective data collection period will vary from one patient to another. At each data entry point all available information since the last data entry occasion should be included in the eCRF.

The descriptive design of this study does not involve any statistical comparisons and does not require a control group.

## **5.3 Study population**

### **5.3.1 Inclusion criteria**

A patient must fulfill the following criteria in order to be included in the study:

1. Patients  $\geq 18$  years of age with a documented PNH diagnosis.
2. Patient started routine treatment with pegcetacoplan for PNH before enrollment or was prescribed pegcetacoplan at enrollment. Decision to initiate treatment shall be made by the treating physician and independently from the decision to include the patient in the study.
3. Patient is willing and able to provide written informed consent to participate in the study in a manner approved by the Institutional Review Board/Independent Ethics Committee and local regulations.

### **5.3.2 Exclusion criteria**

Any of the following will exclude a patient from inclusion in the study:

1. Enrollment in a concurrent clinical interventional study, or intake of an Investigational Medicinal Product (IMP), within three months prior to the start of the current pegcetacoplan treatment.
2. Initiated current treatment with pegcetacoplan in an interventional study.

### 5.3.3 Withdrawal of patients from study

A patient should be withdrawn from the study for any one of the following reasons:

- The patient withdraws consent.
- The patient discontinues treatment with pegcetacoplan.
- The patient enrolls into an interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.

Whenever possible and irrespective of the reason for withdrawal, the date and reason for withdrawal should be recorded in the eCRF. If a patient discontinues due to withdrawal of consent, no new data should be collected after the withdrawal of consent. If the withdrawal is due to any other reason the eCRF should be completed to the extent possible.

If a patient permanently discontinues treatment with pegcetacoplan during the study, the visit where pegcetacoplan is discontinued will be considered the end of study visit. If a patient discontinues pegcetacoplan treatment in-between visits the next scheduled visit will be considered the end of study.

For a patient who enrolls into an interventional study the last routine visit before the enrollment will be considered the end of study visit.

The first routine visit in the interval 21-27 months (24 +/- 3 months) after enrollment will be considered the end of study visit. If a patient has not performed a visit within this interval a later visit can be considered as the end of study visit, as long as this visit does not impact the overall timelines of the study and should occur no later than 24 months + 6 months.

### 5.3.4 Replacement of withdrawn patients

Withdrawn patients will not be replaced.

## 5.4 Treatments

Patients will be prescribed pegcetacoplan, according to clinical practice and investigators judgement. The choice of treatment will not be dictated by the study protocol.

### 5.4.1 Concomitant medication

The protocol does not, in any way, dictate the prescription and intake of any concomitant medication. All therapy considered necessary for the patient's welfare should be given at the discretion of the investigator. PNH related concomitant therapy, such as anticoagulants, erythropoiesis stimulating agents, corticosteroids other immunosuppressive therapies, thrombopoietin receptor agonists, iron chelators should be recorded in the eCRF with dose, start and stop date and route of administration. PNH related concomitant medication should be collected from the pegcetacoplan treatment initiation until the end of study visit.

## 6 Study procedures

### 6.1 Study schedule

#### 6.1.1 Schedule of events

The schedule of events is described in Table 1.

**Table 1** Schedule of events

Data to be collected	Enrollment visit	Routine visits	
		Visits after enrollment up to end of study visit	End of study visit 24 months (+/- 3)*
Informed consent	X		
Review of eligibility criteria	X		
Patient demographics (sex, age, weight and height)	X		
Flow cytometry and C3, AH50, CH50 levels	X	X	X
Relevant medical history	X		
PNH medical history including prior treatments for PNH <sup>1</sup>	X		
Concomitant PNH medication <sup>2</sup>	X	X	X
Transfusions <sup>5</sup>	X	X	X
Dose of pegcetacoplan treatment, including any reason for dose adjustments and reason for discontinuation, if applicable <sup>2</sup>	X	X	X
Acute hemolytic event <sup>2</sup>	X	X	X
Adverse events	X	X	X
Laboratory test results <sup>2,3</sup>	X	X	X
PROs <sup>2,4</sup>	X	X	X
Treatment satisfaction assessed by physician and patient <sup>6</sup>	X	X	X
Health care resource use <sup>5</sup>	X	X	X

Abbreviations: PNH, Paroxysmal nocturnal hemoglobinuria; PRO, Patient reported outcome.

1. Record PNH history that is available in the subject's medical record (see section 7.3.1).

2. Collected from pegcetacoplan treatment start

3. Laboratory test results (see section 7.1.1)

4. PROs: FACIT-Fatigue and QLQ AA/PNH to be captured about twice yearly with approximately 6 months intervals (see section 7.5)

5. Collected from 12 months prior to pegcetacoplan treatment start (see section 7.6)

6. Treatment satisfaction (physician and patient): to be captured about twice yearly with approximately 6 months intervals (see section 7.4.2)

\* Can be performed at a later stage as long as the visit does not impact the overall timelines of the study and should occur no later than 24 months + 6 months (see section 5.3.3)

### **6.1.1.1 Data collected for patients not enrolled in the study**

All patients approached for this study, but not included, should be documented in a screening log/non-enrollment log. Patient characteristics (as applicable according to local regulation) as well as reason for non-participation should be collected in the log.

### **6.1.2 Enrollment visit**

During the enrollment visit, the following assessments should be conducted:

- Documentation of signed informed consent (see section 2.2)
- Review of eligibility criteria

In addition, the following variables will be collected according to routine practice:

- Demographics: age at enrollment, sex, weight, height
- Flow cytometry and C3, AH50 and CH50. See section 7.2
- Relevant medical history. See section 7.3
- PNH medical history including prior treatments for PNH. See section 7.3.1
- Concomitant PNH medication. See section 5.4.1
- Transfusions. See section 7.6
- Dose of pegcetacoplan treatment. See section 7.4.1
- Acute hemolytic event. See section 7.1.3
- Adverse Events. See section 7.7
- Laboratory test results. See section 7.1.1
- PROs see section 7.5:
  - FACIT-Fatigue
  - QLQ AA/PNH
- Patient treatment satisfaction (for patients who started pegcetacoplan treatment at least 3 months before enrollment). See section 7.4.2
- Physician treatment satisfaction (for patients who started pegcetacoplan treatment at least 3 months before enrollment). See section 7.4.2
- Health care resource use. See section 7.6)

### 6.1.3 Routine visits and end of study visit

During routine visits, the following variables will be collected if done so as part of routine medical practice during the 24 (+/-3) month study period, including the last visit of the study (end of prospective period):

- Flow cytometry and C3, AH50 and CH50. See section 7.2
- Concomitant PNH medication. See section 5.4.1
- Transfusions. See section 7.6
- Dose of pegcetacoplan treatment. See section 7.4.1
- Acute hemolytic event. See section 7.1.3
- Adverse Events. See section 7.7
- Laboratory test results. See section 7.1.1
- PROs (see section 7.5):
  - FACIT-Fatigue
  - QLQ AA/PNH
- Patient treatment satisfaction. See section 7.4.2
- Physician treatment satisfaction. See section 7.4.2
- Healthcare resource use. See section 7.6

## 7 Study assessments

### 7.1 Effectiveness assessments

#### 7.1.1 Laboratory test results

The following laboratory test results should be entered in the eCRF if lab samples have been taken as per routine practice by the local laboratory and lab results are available in the medical records:

- Hb
- LDH
- ARC
- Indirect/ total bilirubin



- Haptoglobin
- Ferritin

All available laboratory results for above mentioned tests from closest assessment before pegcetacoplan treatment start and until the end of study visit should be entered in the eCRF.

### **7.1.2 Red blood cell transfusions**

Number of RBC transfusions as well as the RBC units given should be collected from a period of 12 months prior to pegcetacoplan treatment initiation and until the end of study visit.

### **7.1.3 Acute Hemolytic events**

Acute hemolytic event requiring additional intervention as judged by the investigator, should be collected from pegcetacoplan treatment initiation until the end of study. The following information should be entered into the eCRF:

- Start and stop date of acute hemolytic events
- Worsening or occurrence of new clinical PNH related symptoms
- Hb
- Haptoglobin
- ARC
- Indirect/ total bilirubin
- LDH
- Any complement amplifying condition precipitating the acute hemolytic event, as judged by the investigator
- Intervention taken

If the acute hemolytic event is new or worsening and occurring post enrollment, it should also be reported as an adverse event,

## **7.2 Patient/Disease characteristics**

The following information will be collected before pegcetacoplan treatment initiation and thereafter until the end of study. At baseline, the latest information before treatment start should be recorded and the latest information before every routine visit for patients where this information is available in the medical records.

- Coombs test

- PNH clone size assessed by flow cytometry
- Serum C3, AH50 and CH50

### **7.3 Medical History**

Relevant medical history and current comorbidities considered as clinical significant by the investigator should be collected at enrollment and entered in the eCRF.

#### **7.3.1 PNH medical history**

The following PNH history should be collected, if available in the medical records:

- Date of PNH diagnosis including method of diagnosis
- History of Aplastic Anemia
- Previous PNH related treatment 12 months before start of treatment with pegcetacoplan

### **7.4 Treatment-related assessments**

#### **7.4.1 Dose and dosing frequency**

The pegcetacoplan dose, start and stop dates and dosing frequency per patient and reason for dose adjustment and discontinuation should be reported in the eCRF.

If the patient discontinues pegcetacoplan treatment, the reason should be reported as:

- Lack of efficacy
- Treatment tolerability issues
- PNH remission
- Bone marrow transplant
- Other (to be specified).

#### **7.4.2 Treatment satisfaction**

For patients starting pegcetacoplan treatment at least 3 months before enrollment treatment satisfaction should be assessed at the enrollment visit and thereafter every 6 months. For patients starting pegcetacoplan treatment at enrollment the first treatment satisfaction assessment should be performed 6 months after enrollment.

#### **7.4.2.1 Physician treatment satisfaction**

The treating physician will evaluate satisfaction with the pegcetacoplan treatment by answering the question:

"On a scale of 1-5 with 5 being highly satisfied and 1 being highly dissatisfied, how would you rate your satisfaction with the desired treatment outcome of the pegcetacoplan treatment?"

#### **7.4.2.2 Patient treatment satisfaction**

The patient will evaluate satisfaction with the pegcetacoplan treatment by answering the question:

"On a scale of 1-5 with 5 being highly satisfied and 1 being highly dissatisfied, how would you rate your satisfaction with the desired treatment outcome of the pegcetacoplan treatment?"

#### **7.4.3 Previous participation in clinical trials**

If a patient has participated in an interventional clinical trial in the 12 months prior to pegcetacoplan treatment initiation, information such as name of the Investigational product and study participation start and stop dates should be collected.

### **7.5 Patient reported outcomes**

Patient questionnaires will be administered at enrollment and thereafter every 6 months at routine clinical visits to evaluate patients' perceptions of QoL. In addition, if FACIT-Fatigue and/or QLQ AA/PNH questionnaires have been completed by the patient before enrollment and are available at the site, this data will be collected from pegcetacoplan treatment initiation.

It is expected that it will take approximately 15 minutes (every 6 months) to complete both questionnaires.

As with all assessments in a non-interventional study, PROs are not mandatory to complete although it is anticipated that the vast majority of the patients providing consent to participate in the study will agree to complete questionnaires.

#### **7.5.1 FACIT-Fatigue**

FACIT-Fatigue is a 13-item scale developed to assess specifically quality of life concerns related to fatigue in patients with chronic diseases [17, 18]. The scale was initially developed to assess cancer-related fatigue, however it has since then been used and psychometrically validated in other chronic diseases and is routinely used in studies with PNH patients [20]. The instrument includes items such as tiredness, weakness, listlessness, lack of energy, and the impact of these feelings on daily functioning over the past seven days. Each item is scored on a 5-point Likert Scale ranging from "0-Not at all" to "4-Very much". The FACIT-fatigue score is obtained by summing all item scores. The score ranges from 0 to 52, higher score indicating less fatigue and better HRQoL. A 3-point change has been determined as a clinically important change [19].

## 7.5.2 QLQ AA/PNH

The QLQ-AA/ PNH is a relatively newly developed PRO instrument that has been specifically developed to assess QoL in PNH and AA patients according to the EORTC guidelines [21]. Currently, it is the only disease specific QoL instrument available for PNH patients. The questionnaire consists of 54 items relating to how the patient has been feeling lately with 4 response options: 'Not at all', 'A little', 'Moderately' and 'Very'. Scoring guidelines that have been validated for use in clinical studies will be used to calculate patients' scores [21].

## 7.6 Health care resource use

The following data related to health care resource use will be collected for a 12 months pre-pegcetacoplan treatment period and the period following pegcetacoplan treatment initiation at each visit until study end:

- Hospitalizations
- Emergency room visits

## 7.7 Safety assessments

### 7.7.1 Definitions

#### Adverse event (AE)

An AE is any untoward medical occurrence in a patient or study patient administered a pharmaceutical product; the event does not necessarily have a causal relationship with the treatment or usage.

AEs include the following:

- Abnormal test findings\*
- Clinically significant signs and symptoms
- Changes in physical examination findings
- Progression/worsening of underlying disease

\*An abnormal test finding (e.g., abnormal laboratory results, vital signs or ECG) is considered an AE if the finding is associated with accompanying symptoms, leads to a medical/surgical intervention and/or is assessed by the investigator as clinically significant. Abnormal clinically significant lab values assessed by the investigator as part of the natural course of PNH should not be reported as AEs.

In addition, signs and symptoms resulting from the following should also be handled according to the same principles as AEs:

- Overdose
- Withdrawal of treatment
- Interactions
- Abuse
- Misuse

For pregnancies and breastfeeding, see section 7.7.6

### **Preexisting conditions**

A preexisting condition (i.e., a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical examination form) should not be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE reporting period.

### **Serious adverse event (SAE)**

An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death
- Is life-threatening (i.e., at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (i.e., in an offspring to the study patient)
- Is a medically important AE

Medically important AEs are events that may not result in death, be life threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient or patient may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

For the purposes of this study, the following events are considered important medical events and must always be reported as SAEs as outlined in the study protocol:

- Serious infections

### **Hospitalization**

Hospitalization includes transfers within a hospital (e.g. from the psychiatric unit to the intensive care unit) and also includes admissions less than 24 hours. The following situations are not considered hospitalizations (although other SAE criteria may still apply):

- Outpatient procedures/ambulatory care

- Emergency department visits

Hospitalization in the absence of an AE occurring during the study should not be considered an SAE. This includes:

- Hospitalization due to a pre-existing condition not associated with a worsening of the pre-existing condition
- Elective admission, e.g. due to cosmetic surgery
- Pre-planned admission for a condition specified at baseline for the patient

### 7.7.2 Adverse event reporting period

The period for recording AEs in the eCRF begins when the patient signs the ICF and ends at the end of study visit.

### 7.7.3 Eliciting and recording adverse event information

The investigator has to record all AEs in the eCRF using concise medical terminology.

When possible and appropriate, a diagnosis rather than individual signs and symptoms shall be recorded. The investigator is responsible for obtaining sufficient information to determine seriousness, causality and outcome of each AE.

The investigator should ensure all reports are supported by documentation in the patient's medical records.

### 7.7.4 Causality assessment

For AEs collected under this protocol, the investigator must make a causality assessment on the basis of his/her clinical judgement to determine if there is a reasonable possibility that pegcetacoplan caused the AE. The AE is assessed as related or not related to pegcetacoplan with the following definitions:

Related: The AE follows a reasonable temporal sequence from the pegcetacoplan administration and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications).

Not related: The AE does not follow a reasonable temporal sequence from pegcetacoplan administration or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

### 7.7.5 Adverse event reporting

Both serious and non-serious AEs are to be reported on the AE page of the eCRF as specified in the eCRF data entry guidelines.

If an SAE occurs, Global Pharmacovigilance & Patient Safety at Sobi is to be notified by entering required information about the AE into the appropriate module of the eCRF using the designated AE Form within 24 hours of awareness of the event by the investigator.

If the eCRF is not functioning, the SAE can be reported by emailing a completed paper SAE form, using the e-mail address **adverseevent@sobi.com**. The event must be updated electronically in the eCRF by the clinical site once eCRF function resumes. All new information obtained, relevant to an AE report, should be forwarded to Sobi within the same timeframe as the initial information.

The investigator shall provide Sobi with sufficient information to enable a complete medical assessment of the reported event. Best efforts shall be made by the investigator to provide Sobi with additional information related to any AE as requested.

### **7.7.6 Exposure during pregnancy and breastfeeding**

All events of exposure to pegcetacoplan during pregnancy (female patient or male patient's partner) or breastfeeding, shall be reported to Global Pharmacovigilance & Patient Safety at Sobi "by e-mail to **adverseevent@sobi.com**" within 24 hours of awareness by any study personnel, whether the exposure is associated with an AE or not. This includes all situations where a female is or has been found to be pregnant after being exposed to pegcetacoplan; directly, indirectly or via her partner (paternal exposure).

In all reported situations of exposure during pregnancy, Sobi will provide the investigator with a Pregnancy Report Form which shall be completed and returned by the investigator. The investigator is responsible for monitoring the outcome of the pregnancy and to inform Sobi of relevant information and any information requested related to the outcome of the pregnancy.

Before collecting any details on the pregnancy, its outcome and the birth and health of the baby (completing a pregnancy report) a separate consent form should be collected from the mother and/or the father of the child, if required per local regulations. See section 2.2.

Any AE observed in a study participant during and in relation to pregnancy, delivery or breastfeeding should be recorded in the eCRF and as applicable be reported to Sobi as described previously in this section.

### **7.7.7 Follow-up of unresolved adverse events**

All reported AEs should be followed until they are resolved or the investigator assesses them as chronic or stable, or the patient's participation in the study ends, i.e., until the end of study visit. How to report changes in an ongoing AE during a patient's participation in the study is described in the eCRF data entry guidelines.

In addition, all serious and non-serious AEs assessed by the investigator as related to pegcetacoplan should continue to be followed until they resolve or until the investigator assesses them as chronic or stable, even after the patient's participation in the study is over, but without

further recordings into the eCRF. All new information obtained, relevant to an AE report, should be forwarded to Sobi within the same timeframe as the initial information.

The investigator shall provide Sobi with sufficient information to enable a complete medical assessment of the reported event. Best efforts shall be made by the investigator to provide Sobi with additional information related to any AE as requested.

After receipt of the initial report, the information will be reviewed, and the investigator will be contacted to provide additional information or for data clarification. If required, a follow-up report, including all new information obtained on the event, must be prepared and sent to a designated contact for AE reporting. The investigator should ensure all reports are supported by documentation in the patient's medical records. Follow-up reports will be filed as necessary until the event has resolved or attained a stable outcome.

### **7.7.8 Reporting to Regulatory Authorities and IEC/ REB**

Sobi assumes responsibility for appropriate regulatory reporting of AEs/SAEs occurring under treatment with pegcetacoplan reported under this protocol. The investigator is responsible for any reporting of AEs/SAEs to the IEC/ REB as applicable according to local guidelines /legislation.

## **8 Quality control and quality assurance**

This study complies with the definition of a non-interventional (observational) study provided in Article 2 of the EU Clinical Trials Regulation (CTR)[15].

The study will be conducted in compliance with this protocol, applicable Sobi and CRO standard operating procedures (SOP), the ISPE guidelines for GPP [16], the European data protection regulation, GDPR [14] as well as applicable local regulatory requirements.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki [5] and applicable parts of ICH GCP [4] should be followed to safeguard the rights, safety and wellbeing of study patients and to ensure scientific quality.

By signing the protocol (Investigator Protocol Signature Page, stand-alone document 2) the investigator agrees to conduct the study in accordance with the guidelines and regulations mentioned above.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). The investigator will also ensure that this study is conducted in accordance with the local laws and regulations.

The sponsor will systematically review the study quality management to identify, evaluate and control risks to study critical processes and data which would affect patient safety and reliability of study data.



The sponsor will establish a systematic, prioritized, risk-based approach to monitoring and has chosen a combination of on-site and centralized monitoring.

The study site may be subject to a quality assurance audit by Sobi or its representatives, as well as inspection by appropriate regulatory agencies.

Monitoring of the study site will be performed periodically during the study, to help ensure compliance with the protocol, study specific procedures and applicable regulatory requirements. Source documents will be reviewed for verification of agreement with data in eCRFs. All patient ICFs will be reviewed. The investigator or institution guarantees access to source documents by Sobi, its representatives, and appropriate regulatory agencies.

It is important that the investigator(s) and the(ir) relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

Any substantial amendments to this study protocol will be submitted to the IEC/REB for review and approval before implementation, if required by local regulations.

## **9 Statistical plan**

### **9.1 Sample size**

The study plans to include approximately 200 patients from 80 sites.

With a sample size of 200 patients and assuming a standard deviation of 4 g/dL Hb for the change in the primary endpoint, the mean change from baseline will be estimated with a level of accuracy of 0.55 g/dL which would give a sufficient precision for an expected mean change in primary endpoint from baseline of 2-3 g/dL (2.4 g/dL at week 16 in PEGASUS) by keeping the lower limit of the 95% CI above zero. In addition, a sample size of 200 patients would compensate for dropouts during the study while maintaining the lower limit above zero as well as allowing for subgroup analyses.

### **9.2 Definition of study populations**

Full analysis set (FAS) is defined as all enrolled patients.

### **9.3 Overall statistical and analytical plan**

A SAP describing further details of the statistical analyses and subgroups of interest will be prepared prior to enrollment of the first patient.

Statistical analysis will be descriptive with no formal comparison or hypothesis testing performed. Evaluation of data will be based upon descriptive statistics i.e., summary tables and figures. All data will be listed.

## General statistical issues

This non-interventional Phase 4 study is descriptive in nature, and no formal hypothesis testing will be carried out. Patient data will be summarized using descriptive statistics.

Any deviations from the SAP will be documented in the CSR.

Continuous variables will be characterized with non-missing observations, mean and standard deviation, median and interquartile range, minimum and maximum, and number of missing data. Categorical variables will be characterized by the frequency and percent distribution in each category for non-missing data and missing data, as appropriate.

### 9.3.1 Demographics and baseline characteristics

**Disposition:** Frequencies (number and %) of the total number of subjects, discontinued treatment (including reason for discontinuing treatment) will be tabulated and listed.

**Demographics:** Demographic data will be summarized by descriptive statistics.

Baseline will be defined as initiation of pegcetacoplan (start date of pegcetacoplan treatment).

### 9.3.2 Analysis related to primary objective

The change in observed Hb levels from initiation of treatment with pegcetacoplan to 6 months will be presented by descriptive statistics for patients treated with pegcetacoplan for at least 6 months. In addition, a regression model will be used to adjust for clinically important variables such as baseline Hb, sex and age. The estimated mean change from baseline together with the corresponding 95% CI will be presented.

A sensitivity analysis of the primary analysis will be performed excluding patients who received RBC transfusions within 6 months from initiation of treatment with pegcetacoplan.

### 9.3.3 Secondary endpoints supporting the primary objective

The change in laboratory values at initiation of pegcetacoplan treatment to 6 months for LDH, ARC, Indirect/total bilirubin, Haptoglobin and Ferritin will be using the same approach as for the primary analysis.

Laboratory values at initiation of pegcetacoplan treatment and each 6 months until end of study for Hb, LDH, ARC, Indirect/total bilirubin, Haptoglobin and Ferritin will be tabulated and presented with descriptive statistics. A graphical overview of the laboratory values will be displayed as applicable.

#### **Hemoglobin $\geq 12$ g/dL**

The proportion of patients with Hb  $\geq 12$  g/dL at initiation of pegcetacoplan treatment and each 6 months until end of study period will be presented with descriptive statistics.

#### **Increase in hemoglobin levels of $\geq 2$ g/dL**

The proportion of patients with an increase of Hb levels  $\geq 2$  g/dL at each 6 months until end of study period compared to baseline will be presented with descriptive statistics.

#### **Acute hemolytic event requiring additional intervention**

The proportion of patients with acute hemolytic event requiring additional intervention at initiation of pegcetacoplan treatment and each 6 months until end of study period will be presented with descriptive statistics.

#### **Annualised number of red blood cell transfusions and units**

The annualised number of RBC transfusions and units 12 months before and during pegcetacoplan treatment until end of study will be calculated separately and presented with descriptive statistics.

### **9.3.4 Analysis related to secondary objective**

The questionnaires used in this study are: FACIT-Fatigue and QLQ AA/PNH.

The FACIT Fatigue Scale is a 13-item Likert scaled instrument assessing the level of patient's fatigue. The 5 possible responses are 'Not at all' (0), 'A little bit' (1), 'Somewhat' (2), 'Quite a bit' (3) and 'Very much' (4). With 13 statements the total score has a range of 0 to 52. The scores will be summarized and presented by descriptive statistics at initiation of treatment with pegcetacoplan and every 6 months until end of study [17, 18, 19, 20].

The QLQ AA/PNH questionnaire consists of 54 items. Scoring guidelines will be used to calculate patients' scores. The scores will be summarized and presented by descriptive statistics at initiation of treatment with pegcetacoplan and every 6 months until end of study [21].

Annualized number of hospitalizations and emergency room visits, in the 12 months before pegcetacoplan treatment until end of study will be presented separately with descriptive statistics.

Patient treatment satisfaction and physician treatment satisfaction (5-point scale) at each 6 months until end of study will be tabulated and presented by descriptive statistics.

### **9.3.5 Analysis of safety and tolerability data**

#### **9.3.5.1 Adverse events**

Reported AEs during the study will be coded using the medical dictionary for regulatory activities (MedDRA). The incidence of AEs will be summarized in frequency tables, by system organ class, preferred term and by causality assessment. Separate tabulations will be performed for serious and non-serious AEs.

### **9.3.6 Interim analysis**

Interim analyses of data will be performed during the study duration. The first interim analysis will include at least 30 patients. The subsequent interim analyses will not be carried out more often than every six months. The purpose of the interim analyses is to share the data with the PNH community.

### **9.3.7 Exploratory subgroup analyses**

Additional details, including subgroups of interest, will be described in the associated SAP.

### **9.3.8 Handling of missing data**

Missing data will not be imputed. Missing dates might be imputed according to the procedures described in the SAP. Other missing data will not be imputed.

## **10 Data collection, handling and record keeping**

### **10.1 Data standards**

Collection of data should be performed in the clinical data acquisition standards harmonization (CDASH) format, according to the clinical data interchange standards consortium (CDISC). The standards should be used to the extent possible and/or required for the specific study/project. The minimum requirement of the CDISC standard is to collect all core variables specified as 'Required' in the study data tabulation model (SDTM) format.

### **10.2 Case report form**

An eCRF is required and should be completed for each included patient. In this study an electronic eCRF will be used. Only authorized personnel will have access to the eCRF. Data will be entered into eCRFs in accordance with eCRF data entry guidelines. Each investigator is responsible for ensuring that accurate data are entered into the eCRF in a timely manner. The completed original eCRFs are the sole property of Sobi and should not be made available in any form to third parties without written permission from Sobi, except for authorized representatives of appropriate Regulatory Authorities.

On-line logic checks will be built into the electronic data capture (EDC) system, so that missing or illogical data are not submitted. In the event that inconsistent data persist, queries may be issued via the eCRF to the study center and answered electronically by that study center's personnel. The identifying information (assigned username, date, and time) for both the originator of the query and the originator of the data change (if applicable), as well as the

investigator's approval of all changes performed on the data, will be collected. All entries and changes in the eCRF will be tracked via an audit trail.

It is the responsibility of the investigator to ensure completion and to review and approve all eCRFs. ECRFs must be signed by the investigator. These signatures serve to attest that the information contained on these eCRFs is correct. At all times, the investigator has final responsibility for the accuracy and authenticity of all data entered on the eCRFs.

### **10.3 Source data**

Patient source documents are the physician's patient records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. In those cases, the information collected on the eCRFs must match those charts.

For collected PRO data, e.g., the actual/original forms completed by the patients are considered as source documents.

The following data may use the eCRF as source:

- Patient and physician treatment satisfaction
- AE causality assessment

A source data location document will be completed by each site. This document will specify the source document for each collected data point.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

### **10.4 Protocol deviations**

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of patients. The investigator should not implement any deviation from, or changes of, the protocol unless it is necessary to eliminate an immediate hazard to study patients.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

When a deviation from the protocol is identified, the investigator or designee must ensure the CRO is notified. The CRO will follow up with the investigator, as applicable, to assess the

deviation and the possible impact to the safety and/or efficacy of the patient to determine patient continuation in the study.

The Investigator and CRO must contact Sobi immediately if a deviation is discovered that significantly affects or has the potential to significantly affect human patient protection or the reliability of study results.

The investigator will also assure that deviations are reported and documented in accordance with IEC/REB and applicable regulatory requirements.

## **10.5 Database closure**

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The study database must be locked before generation of any results. The database lock will be approved by relevant study personnel, and all edit accesses will be removed.

## **10.6 Record retention**

The investigator should maintain a record of the location(s) of investigator's essential documents as defined in the ICH GCP Guideline [4] including source documents and should have control of and continuous access to all essential documents and records generated by the investigator/institution before, during, and after the study.

All documents and data relating to the study will be kept securely by the investigator in a secure file and/or electronically. The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search and retrieval. The data will be available for evaluation and/or audits from Regulatory Authorities and IEC/REB, Sobi or Sobi's representatives.

When a copy is used to replace an original document (e.g., source documents, eCRF), the copy should fulfill the requirements for certified copy as defined in ICH GCP Guideline [4].

The records should be retained by the investigator as specified in the Clinical Trial Agreement and in accordance with local regulations.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator or another institution. Archiving on behalf of the investigator can also be delegated to Sobi.

## **11 Discussion on study design**

There is a need to provide data to treaters and the PNH community on the real-world usage and effectiveness of pegcetacoplan. This study aims to fill part of that knowledge gap and to add to the knowledge base regarding the use of pegcetacoplan in routine PNH treatment.

For the purpose of the above an observational study design was adopted to capture data on pegcetacoplan use in the real-world setting. The eligibility criteria were selected to allow for inclusion of a broad group of PNH patients treated with pegcetacoplan. Achieving the target sample size is dependent on the number of PNH patients who are prescribed pegcetacoplan treatment.

The limited number of eligibility criteria in combination with the planned sample size and enrollment at a high number of sites in several countries provides an overview of PNH patients which may be considered representative of the general population of adult PNH patients.

As per guidelines for safety data collection for orphan diseases, all adverse events will be collected within this protocol [23].

## **11.1 Appropriateness of effectiveness measurements**

PNH is characterized by hemolytic breakdown of erythrocytes, which is manifested by changes in several laboratory markers. Hb is the most direct indicator of clinical severity in hemolytic diseases and essential for evaluation of treatment response. Reduced Hb levels indicate increased hemolytic activity.

LDH is an intracellular enzyme which increases in plasma in connection with erythrocyte breakdown. In hemolytic conditions, LDH is often increased and may be used to distinguish EVH, being slightly increased in the former and 4-5-fold the UNL in the latter.

Reticulocytes are immature erythrocytes, normally representing a small fraction of peripheral RBCs. The ARC increases when there is an increased production of erythrocytes, as in connection with hemolysis and anaemia. In PNH, the reticulocyte counts may remain elevated during treatment because of persistent hemolysis.

Bilirubin is a breakdown product of Hb and circulates in plasma tightly bound to albumin (measured as indirect or unconjugated bilirubin). In the liver, bilirubin is enzymatically conjugated and then excreted with the bile (direct, or conjugated bilirubin). Increased bilirubin levels due to increased Hb catabolism results in increased unconjugated hyperbilirubinemia, whereas decreased hepatic clearance most commonly results in conjugated hyperbilirubinemia. Thus, in connection with hemolysis, total bilirubin in plasma as well as the proportion of indirect (or unconjugated) bilirubin increases. Bilirubin is a good marker for EVH and, to a lesser extent, also for IVH.

Haptoglobin is a glycoprotein acting as a scavenger by binding free circulating Hb released by hemolysis or normal erythrocyte turnover. Haptoglobin is significantly decreased during hemolysis.

Ferritin is an intracellular storage protein for iron, which may be used as an indirect marker of the total body amount of iron. Patients with PNH may display either increased ferritin values because of continuous EVH or reduced ferritin levels due to iron loss. Moreover, increased ferritin levels may be caused by iron overload after multiple transfusions. In addition, ferritin is an acute phase protein and increases in connection with inflammatory conditions.

To assess the effectiveness of pegcetacoplan treatment the change in laboratory values will be assessed from treatment start until month 6. Thereafter, laboratory values will be analysed at 6 month intervals to describe the maintenance of treatment effectiveness.

## **11.2 Bias and Limitations of the study**

This observational study is descriptive and carries the general limitations inherent in an observational design relying on information collected under real world conditions.

PNH treatment centers in Europe, Canada, Middle East and Australia will be invited by Sobi to participate in the study.

Sobi intends to include a high number of sites (80) in several countries. However, because the participating sites comprise a population of volunteers, a non-response selection bias is possible, and the final sample of investigators may not be perfectly representative. All centers approached, but not included in the study will be documented.

The investigators will attempt to enroll all eligible patients who present for a routine visit . All patients approached for this study, but not included, should be documented in a pre-screening log/non-enrollment log, including reason for non-participation. To avoid potential bias in selection of the patient population, the patient selection criteria allow for the absolute majority of patients at the participating sites to be enrolled.

Relying on investigators to fill out the assessment forms might result in missing data, which can result in bias. Data collected retrospectively may not be as well documented as prospective data. Entry of data in eCRFs will minimize missing or incorrect data through automatic or manual data checks.

As PROs are not mandatory to complete, QoL variables may be biased as patients agreeing to PRO completion may differ from those choosing not to complete PROs. In addition, as pegcetacoplan treatment may be initiated prior to study enrollment, PRO data at the time of pegcetacoplan treatment start, may not be available for all patients. For patients who do not have any PRO data at pegcetacoplan treatment start, it will not be possible to assess treatment related changes in QoL.

## **12 End of study**

The end of this study is defined as the date of last patient out, i.e., the last patient's last visit.

## **13 Sponsor's discontinuation criteria**

Sobi reserves the right to discontinue the study prior to inclusion of the intended number of patients but intends only to exercise this right for valid scientific, ethical or administrative reasons. After such a decision, the investigator must inform all participating patients at their next



routine visit to the site. All study materials must be collected and all the eCRFs completed to the greatest extent possible.

## **14 Dissemination and publication of results**

Sobi will post study information by registering the study on the publicly accessible website [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

Sobi is committed to publishing study results in a complete, accurate, balanced, transparent and timely manner. Sobi follows the principles of the International Committee of Medical Journal Editors (ICMJE) recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals including criteria for authorship [24].

The data from this study will be considered for reporting at a scientific meeting or for publication in a scientific journal. The sponsor will be responsible for these activities and will work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues. The results of the study, or any part thereof, shall not be published without the prior written consent and approval of Sobi, such consent and approval not to be unreasonably withheld.

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**Appendix 1****List of stand-alone documents**

<b>Number</b>	<b>Title</b>	<b>Document reference; version or date</b>
<i>1</i>	Protocol Signature Page	version 2.0, 24 January 2024
<i>2</i>	Investigator Protocol Signature Page	version 2.0, 24 January 2024
<i>3</i>	List of Responsible Parties	version 2.0, 24 January 2024

## Protocol Signature Page

### Stand-alone document 1

**A single arm, multicentre observational study to evaluate effectiveness of pegcetacoplan under real world conditions in patients with paroxysmal nocturnal hemoglobinuria (PNH)**

Protocol Number: **Sobi.PEGCET-304**

Short title: **COMPLETE**


Type of Study: **Non-Interventional Study**

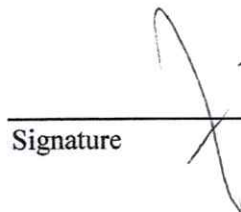
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 27 January 2024  
Signature Date

 29/01/2024  
Signature Date