A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Cold Agglutinin Disease (CAD)

Final Protocol Number: **Sobi.PEGCET-101**

EudraCT Number: **2021-003160-27**

Type of Study: **Therapeutic Confirmatory**

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Sponsor's Medical Director

[redacted]
Medical Director
[redacted]

Signature Date

Principal Coordinating Investigator

[redacted]

Signature Date

Investigator statement

I have read the protocol entitled "A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Cold Agglutinin Disease (CAD)" and the accompanying current investigator's brochure. I agree to conduct the clinical investigation in compliance with the Final Protocol, Version 4.0, 28 Apr 2022, the International Council for Harmonisation (ICH) harmonised guideline E6(R2): Guideline for Good Clinical Practice (GCP) [1], applicable regulatory/government regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki [2]. I will not implement any changes to study procedures or conduct without prior approval from the sponsor and, when applicable, the independent ethics committee/institutional review board/research ethics board and regulatory authority. I will supervise any individual or party to whom I delegate study-related duties and functions conducted at the study site and ensure qualification of individuals or parties who perform delegated tasks.

I agree to maintain the confidentiality of this study protocol, as described on the title page. Further, I will not publish results of the study without authorization from Swedish Orphan Biovitrum AB (publ).

My site has implemented risk minimization and the mitigation plan for COVID-19 in line with local regulations and best practices, including precautions such as the use of personal protective equipment for patients, site staff and other visitors, site staff health-check and the disinfection of site premises.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

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1 Synopsis

STUDY IDENTIFIERS	
Title of study:	A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with Cold Agglutinin Disease (CAD)
Clinical study number:	Sobi.PEGCET-101
Type of study:	Therapeutic confirmatory
STUDY OBJECTIVES	
Primary objective:	To demonstrate the efficacy of twice-weekly subcutaneous (s.c.) 1080-mg infusions of pegcetacoplan compared with that of placebo in patients with CAD.
Secondary objectives:	*Key secondary objectives:* • To demonstrate the effect of pegcetacoplan on the number of packed red blood cell (PRBC) transfusions in patients with CAD. • To demonstrate the effect of pegcetacoplan on health-related quality of life in patients with CAD. *Other secondary objectives:* • To assess the effect of pegcetacoplan on clinical laboratory markers of hemolysis and transfusion dependence in patients with CAD. • To determine the durability of response in patients with CAD receiving pegcetacoplan. • To assess tolerability, safety and immunogenicity of pegcetacoplan in patients with CAD. • To describe long-term effect of pegcetacoplan in patients with CAD.
Exploratory objectives:	• To evaluate the pharmacokinetics (PK) of pegcetacoplan following twice-weekly s.c. infusions. • To evaluate the effect of pegcetacoplan in complement biomarkers.
STUDY ENDPOINTS	
Primary endpoint:	Response to treatment at Week 24. Response is defined as: • An increase in hemoglobin (Hb) of ≥ 1.5 g/dL from Baseline or Hb normalization at Week 16; AND • Maintenance of this effect from Week 16 to Week 24; AND • The absence of PRBC transfusions (between Week 5 and Week 24). Note: Hb normalization is defined as within normal range (between the defined upper and lower limits of normal [ULN and LLN]), as set by the testing laboratory.
Key secondary endpoints:	• Change from Baseline to Week 24 in Hb level. • Transfusion avoidance (Yes/No) from Week 5 to Week 24. • Change from Baseline to Week 24 in the Functional Assessment of Cancer Therapy–Anemia/Fatigue (FACT-An) score.

Secondary efficacy endpoints:

Part A:

- Number of PRBC transfusions from Week 5 to Week 24.
- Change from Baseline to Week 24 in the following:
  - Lactate dehydrogenase (LDH) level.
  - Haptoglobin level.
  - Indirect bilirubin level.
  - Absolute reticulocyte counts (ARC).
  - D-dimer level.
- Normalization of markers of hemolysis at Week 24, specifically:
  - LDH level.
  - Indirect bilirubin level.
  - ARC.
- Time to first normalization from Baseline to Week 24 for the following:
  - Hb level.
  - LDH level.
  - Indirect bilirubin level.
  - ARC.
- Number of PRBC units transfused from Week 5 to Week 24.
- Change from Baseline to Week 24 in the following:
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale score of the FACT-An scale.
  - 12-Item Short Form Survey (SF-12) score.
  - 5-Level EuroQol 5-Dimension (EQ-5D-5L) score.

Part B:

- Change from Baseline to Week 48 in the following:
  - Hb level.
  - LDH level.
  - Haptoglobin level.
  - Indirect bilirubin level.
  - ARC.
  - D-dimer level.
- Normalization of markers of hemolysis at Week 48, specifically:
  - LDH level.
  - Indirect bilirubin level.
  - ARC.
- Durability of response for patients randomized to pegcetacoplan who achieve the primary endpoint at Week 24.
- Change from Baseline to Week 48 in the following:
  - FACT-An score.
  - FACIT-F subscale score of the FACT-An scale.
  - SF-12 score.
  - EQ-5D-5L score.

Tertiary efficacy endpoints:	Part C:
	• Change from Baseline to Week 96 in the following:
	  • Hb level.
	  • LDH level.
	  • Haptoglobin level.
	  • Indirect bilirubin level.
	  • ARC.
	  • D-dimer level.
	• Normalization of markers of hemolysis at Week 96, specifically:
	  • LDH level.
	  • Indirect bilirubin level.
	  • ARC.
	• Change from Baseline to Week 96 in the following:
	  • FACT-An score.
	  • FACIT-F subscale score of the FACT-An scale.
	  • SF-12 score.
	  • EQ-5D-5L score.

Safety endpoints:	• Adverse events (AEs) up to 8 weeks after end of treatment (EOT). • Serious adverse events (SAEs) up to 8 weeks after EOT. • AEs leading to premature discontinuation of the investigational medicinal product (IMP). • Clinically meaningful laboratory abnormalities up to 8 weeks after EOT. • Changes from Baseline in laboratory parameters markers (Baseline will be taken as the last measurement prior to the first dose of IMP). • Clinically meaningful electrocardiogram abnormalities up to 8 weeks after EOT. • Clinically meaningful changes in vital signs from Baseline up to 8 weeks after EOT. • Immunogenicity: presence of antibodies (Ab) to polyethylene glycol and pegcetacoplan peptide throughout treatment and follow-up periods.
Exploratory endpoints:	• Pegcetacoplan pharmacokinetic concentrations at Week 24 and Week 48. • Changes from Baseline to Week 24 and Week 48 in complement biomarkers (C3 levels, functional assays for classical and alternative complement pathways). • Changes from Baseline through Week 24 and Week 48 in C3 deposition on RBCs by flow cytometry. • Changes from Baseline to Week 24 and Week 48 in inflammatory biomarkers: TNFα, IL-6, IL-10, IFNγ and IL-1β. • Normalization of haptoglobin level at Week 24, Week 48 and Week 96. • Time to first normalization from Baseline to Week 24 for haptoglobin level.

STUDY DESIGN AND METHODS

Study design:

This is a phase 3, randomized, double-blind, placebo-controlled multicenter study of s.c. pegcetacoplan 1080 mg twice weekly or placebo conducted in 57 patients with CAD.

Patients will be randomized in a ratio of 2:1 to receive either pegcetacoplan or placebo, respectively. The randomization will be stratified by transfusion history (number of transfusions during the 6-month period prior to randomization ≥ 1; 0). Every effort should be made to enroll patients in both subgroups.

The planned length of participation in the study for each patient is a maximum of 104 weeks. This study will consist of 5 periods:

- Screening period: up to 4 weeks.
- Double-blind treatment period: 24 weeks (Part A).
- Open-label treatment period: 24 weeks (Part B).
- Open-label maintenance period: up to additional 48 weeks or until the product becomes commercially available (Part C).
- Follow-up period: 8 weeks.

Screening period (up to 4 weeks)

Informed consent will be obtained during a screening visit prior to any study-related procedures being conducted. Some screening assessments, including laboratory tests and quality of life questionnaires, will be performed within 7 days before randomization. Patients will be screened to confirm that the patient selection criteria for the study have been met. Key inclusion and exclusion criteria will be reviewed by the study medical monitor and eligibility will be confirmed prior to the enrollment. Patients experiencing acute hemolytic crisis may receive blood cell transfusions during the screening period.

Double-blind treatment period (24 weeks): Part A

A total of 57 patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 2:1 ratio to either pegcetacoplan or placebo. Safety and efficacy will be assessed.

Patients randomized into the study will receive s.c. IMP (pegcetacoplan or placebo) twice weekly for 24 weeks.

All standard-of-care medications can be continued, with the exception of protocol-defined prohibited medications.

During the double-blind treatment period, patients will receive a blood transfusion if Hb level is ever shown to be < 7.0 g/dL. During this study period, transfusion will be considered, at the investigator's discretion, in symptomatic patients with Hb levels ≥ 7.0 and < 9.0 g/dL.

Open-label treatment period (24 weeks): Part B

All patients who complete the 24-week double-blind treatment will be eligible to enter the open-label treatment period, in which they will receive pegcetacoplan 1080 mg s.c. twice weekly for up to 24 weeks (Week 48).

Open-label maintenance period (up to additional 48 weeks or until the product becomes commercially available): Part C

After completion of the open-label treatment period, patients who benefit from therapy without significant side effects will continue receiving pegcetacoplan 1080 mg s.c. twice weekly for a maximum of 48 additional weeks or until the product is commercially available.

	Follow-up period (8 weeks) After completion of the open-label maintenance period, or if patients discontinue pegcetacoplan treatment early, an EOT visit will be performed, followed by an end of study visit 8 weeks later. No formal interim analyses are planned. However, data will be reported for Part A (double-blind treatment period) once all patients have completed their Week 24 visit (or have early discontinued) and the database has been cleaned and verified for all visits up to and including Week 24. Similarly, data will be reported after Part B.
Number of patients planned:	57 patients.
Diagnosis and main criteria for inclusion:	Patients with a diagnosis of primary CAD. Inclusion criteria: 1. Age18 years or older. 2. Diagnosis of primary CAD on the basis of the presence of **all** the following criteria: a. Signs of hemolysis with abnormal values by at least 2 of the following hemolytic markers: i. Reduced haptoglobin level (< LLN). ii. Elevated LDH level (> ULN). iii. Elevated indirect bilirubin level (> ULN; > 3 x ULN for patients with Gilbert-Meulengracht Syndrome). iv. Increased ARC (above the ULN). b. Monospecific direct antiglobulin test strongly positive for C3d. c. Cold agglutinin titer ≥ 64 at 4 °C. 3. Hb level ≤ 9 g/dL. 4. An absolute neutrophil count ≥ 1500 cells/mm^3 at screening. 5. Documented results from bone marrow biopsy within 1 year of screening with lymphoproliferative infiltration ≤ 20 %. Patients who have not received a bone marrow biopsy within 1 year of their screening visit or those patients for whom bone marrow biopsy reports are incomplete or unavailable will be required to receive a bone marrow biopsy to determine eligibility. 6. Body weight ≤ 100 kg. 7. Either have vaccination against *Streptococcus pneumoniae*, *Neisseria meningitidis* (Types A, C, W, Y, and B), and *Haemophilus influenzae* (Type B) within 2 years prior to screening or agree to receive vaccination during screening as follows: a. First dose of vaccine against *N. meningitidis* Types A, C, W, and Y at least 2 weeks prior to start of study drug with second dose 2 months later (Study Day 57), and then boosters every 5 years. b. First dose of the vaccine against *N. meningitidis* Type B at least 2 weeks prior to start of study drug with a second dose after at least 1 month (Study Day 29). First booster dose 1 year later, and then additional booster doses every 2 to 3 years. c. *S. pneumoniae:* pneumococcal conjugate vaccine 13 (PCV13) and/or pneumococcal polysaccharide vaccine 23 (PPSV23) as per Advisory Committee on Immunization Practices (ACIP)

guidelines for adults or children with immunocompromising conditions.

d. *H. influenzae* Type B: 1 dose at least 2 weeks prior to start of study drug.

Vaccination is mandatory, unless documented evidence exists that patients are nonresponders to vaccination. Patients who were not previously vaccinated should not receive multiple vaccines on the same day.

8. Women of childbearing potential (WOCBP), defined as any women who have experienced menarche and who are NOT permanently sterile or postmenopausal, must have a negative pregnancy test at screening and agree to use protocol-defined methods of contraception for the duration of the study and 8 weeks after their last IMP dose.

   Note: Postmenopausal is defined as having had 12 consecutive months with no menses without an alternative medical cause.

9. Men must agree to the following for the duration of the study and 8 weeks after their last IMP dose:
   a. Avoid fathering a child.
   b. Use protocol-defined methods of contraception.
   c. Refrain from donating sperm.
10. Willing and able to give written informed consent.

Exclusion criteria:

1. Have received other anticomplement therapies (approved or investigational) within 5 half-lives of the agent prior to randomization (e.g., eculizumab within 10 weeks, ravulizumab within 36 weeks or sutimlimab within 4 weeks) and are not able or willing to refrain from using them during the study.
2. Treatment with rituximab monotherapy within 12 weeks prior to randomization, or rituximab combination therapies (e.g., with bendamustine, fludarabine, other cytotoxic drugs or ibrutinib) within 16 weeks prior to randomization.
3. Use of prohibited medications as described in the protocol. The list of acceptable medications and required stable regimen periods are outlined in the study protocol.
4. Diagnosis of systemic lupus erythematosus or other autoimmune diseases with antinuclear antibodies.
5. History of an aggressive lymphoma or presence of a lymphoma requiring therapy.
6. Have received an organ transplant.
7. Cold agglutinin syndrome secondary to *Mycoplasma pneumoniae*, Epstein-Barr virus or other specific causative infection.
8. HIV or hepatitis C virus detectable by polymerase chain reaction at screening or documented in the patient's medical record.
9. Chronic inactive hepatitis B virus with viral loads > 1000 IU/mL (> 5000 copies/mL) at screening or documented in the patient's medical record. Eligible patients who are chronic active carriers (≤ 1000 IU/mL) must receive prophylactic antiviral treatment (e.g.,

	entecavir, tenofovir, lamivudine) according to local country guidelines. 10. Presence of an active malignant disease within the last 12 months other than skin basal cell carcinoma or in situ carcinoma of the cervix. A low-grade lymphoproliferative bone marrow disorder not requiring therapy by itself is not defined as a malignant disease in this context. 11. A monospecific direct antiglobulin test result of IgG > 1+. 12. Presence or suspicion of liver dysfunction as indicated by elevated alanine aminotransferase (ALT) > 2.5 x ULN, or direct bilirubin levels > 2 x ULN. 13. Hypersensitivity to pegcetacoplan or to any of the excipients or placebo compounds. 14. Known or suspected hereditary fructose intolerance. 15. Unresolved infection caused by encapsulated bacteria including *N. meningitidis*, *S. pneumoniae* and *H. influenzae*. 16. Presence or suspicion of severe recurrent or chronic infections that, in the opinion of the investigator, increase the patient's risk by participating in the study. 17. Participation in any other investigational drug trial or exposure to other investigational agent, device or procedure within 30 days prior to screening period. 18. If breastfeeding, is unwilling to discontinue for the duration of study and for at least 8 weeks after the final IMP dose. 19. Inability to cooperate with study procedures. 20. Any disease(s), psychiatric condition, metabolic dysfunction, or findings from a physical examination or clinical laboratory test result that would cause reasonable suspicion of a disease or condition that may jeopardize the patient's wellbeing, that may increase the risk associated with study participation, that may affect the interpretation of the results, or that would make the patient unsuitable for this study. 21. Protected adults (guardianship, trusteeship) who are unable to express their consent and persons under court protection.
Assessments:	Refer to the schedule of assessments (Table 1 and Table 2).
Test product; dose and mode of administration:	Pegcetacoplan, 1080 mg twice weekly, s.c. infusion (20 mL).
Reference product; dose and mode of administration:	Placebo, twice weekly, s.c. infusion.
Duration of treatment(s):	Up to 96 weeks (Part A – double-blind treatment period: 24 weeks; Part B – open-label treatment period: 24 weeks; Part C – open-label maintenance period: up to 48 weeks).

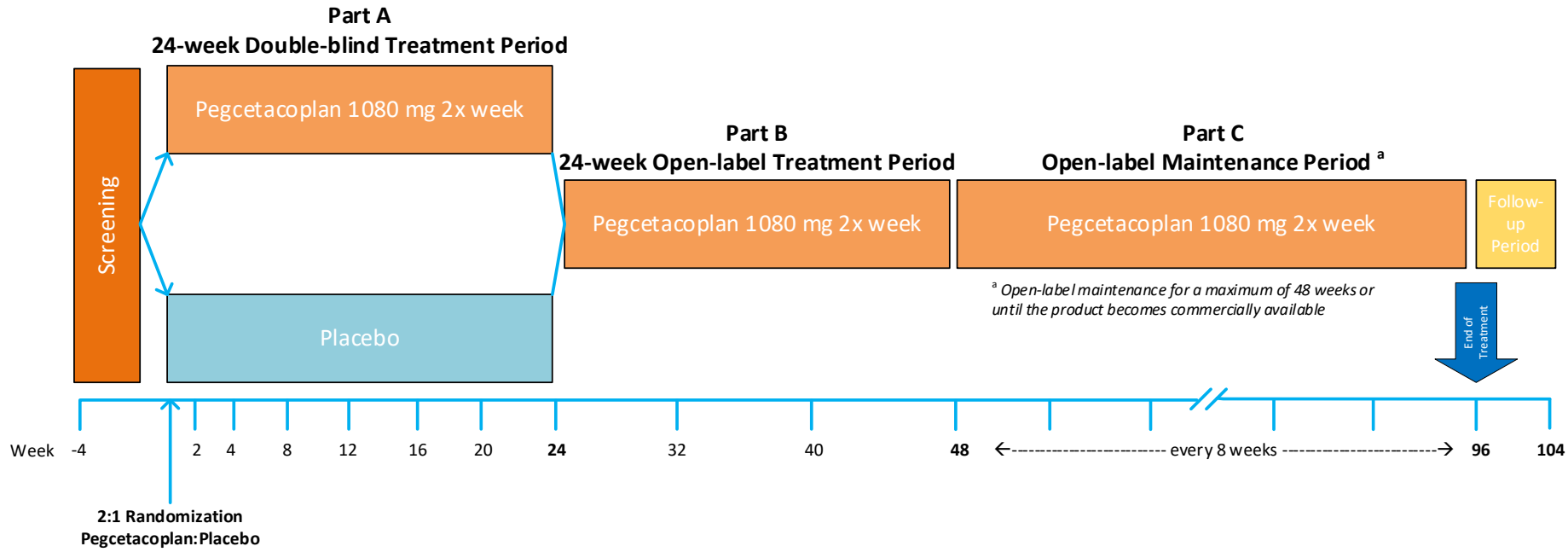
Determination of sample size:	The primary endpoint is response at Week 24. Under the assumption that the response rate is 55 % for pegcetacoplan and 10 % for placebo, 54 patients (36 treated with pegcetacoplan and 18 with placebo) are required to reject the null hypothesis of no difference between the treatment groups at a significance level of 5 % and a power of 90 % using a 2-sided Fisher's exact test with a 2:1 allocation to treatment groups. To account for potential drop out prior to first dose of IMP, 57 patients will be enrolled in the study.
Statistical methods:	The primary efficacy endpoint is a responder analysis, where response is defined as an increase in Hb level of ≥1.5 g/dL from Baseline or Hb normalization, and maintenance of this effect from Week 16 to Week 24, in the absence of PRBC transfusions (between Week 5 and Week 24). The estimand will be a composite where patients having an intercurrent event will be considered as nonresponders. The intercurrent events of interest are: • Withdrawal from treatment or lost to follow-up before end of the double-blind period. • Use of prohibited medications (any therapy for CAD including rituximab alone or in combination; any other complement inhibitor; any other investigational drug and plasma exchange). The number and percentage of patients who respond will be tabulated by treatment group and compared between treatment groups using a Fisher's exact test. The odds ratio of being a responder for the pegcetacoplan treatment group versus the placebo group and associated 95 % confidence interval (CI) will be provided. The change from Baseline to Week 24 in Hb will be analyzed using mixed-model for repeated measures (MMRM) with the fixed effects of treatment, strata, visit, visit-by-treatment interaction and Hb level at Baseline as covariate, using an unstructured covariance matrix and the Kenward-Roger method for calculating the degrees of freedom. The difference between treatment groups will be estimated, along with its 95 % CI and p-value. Transfusion avoidance will be tabulated by treatment group and compared between treatment groups using Fisher's exact test. The odds ratio of showing transfusion avoidance from Week 5 to Week 24 for the pegcetacoplan treatment group versus the placebo group and associated 95 % CI will be provided. The composite strategy is used as estimand where patients meeting any of the intercurrent events defined for primary endpoint will be considered as failures. The change from Baseline at Week 24 in the FACT-An score will be analyzed using MMRM with the fixed effects of treatment, strata, visit, visit-by-treatment interaction and the FACT-An score at Baseline as covariate, using an unstructured covariance matrix and the Kenward rogers method for calculating the degrees of freedom. The difference between treatment groups will be estimated, along with its 95 % CI and p-value. To preserve the Type 1 error, a fixed-sequence testing strategy will be used; hence, statistical significance with the first key secondary endpoint will only be concluded if statistical significance is achieved with the primary analysis of the primary endpoint. The order of testing the key secondary endpoints will be: • Change from Baseline to Week 24 in Hb level. • Transfusion avoidance (Yes/No) from Week 5 to Week 24. • Change from Baseline to Week 24 in the FACT-An score. The hierarchical testing will be applied to the primary and key secondary endpoints, no further multiplicity control will be applied.

All efficacy (primary and secondary) analyses will be conducted on the intent-to-treat set.

All safety analyses will be carried out descriptively on the safety set, consisting of all patients who received at least 1 dose of IMP.

Study schematic

Figure 1 Study design



Schedule of assessments

Table 1 Schedule of assessments: Screening to Week 24 – Part A

Study Period	**Screening [a]**		**Part A: Double-blind treatment period**								
Study Week	**-4 to -1**	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**
Study Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**
Study Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit window (± days)	**0**		**0**	**1**	**2**	**7**	**7**	**7**	**7**	**7**	**7**
Informed consent	X										
Demographics	X										
Medical history	X										
RBC transfusions collection	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion criteria	X	X	X								
Randomization			X								
Vaccination [b]	X				X			X			
Prophylactic antibiotic administration [c]	According to local standard practices in patients who cannot be vaccinated										
Full physical examination [d]	X		X								X
Brief physical examination [e]				X	X	X	X	X	X	X	
Weight and height [f]	X		X	X	X	X	X	X	X	X	X
12-lead ECG (prior to venipuncture)	X		X								X
IMP administration [g]			Twice weekly----------→								
Infusion-site assessment [h]			X	X	X	X	X	X	X	X	X
Concomitant medications/treatments	X		X	X	X	X	X	X	X	X	X
Vital sign measurements [i]	X		X	X	X	X	X	X	X	X	X
Urine studies		X				X	X	X	X	X	X
Blood [k]	X	X		X	X	X	X	X	X	X	X

Table 1 Schedule of assessments: Screening to Week 24 – Part A

Study Period	**Screening [a]**		**Part A: Double-blind treatment period**								
Study Week	**-4 to -1**	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**
Study Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**
Study Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit window (± days)	**0**		**0**	**1**	**2**	**7**	**7**	**7**	**7**	**7**	**7**
Pharmacokinetics [m]		X		X	X	X		X			X
Anti-pegcetacoplan peptide and anti-PEG Ab assay [n]		X		X	X	X		X			X
Hematology		X		X	X	X	X	X	X	X	X
Serum chemistry		X		X	X	X	X	X	X	X	X
Coagulation profile [o]		X		X	X	X	X	X	X	X	X
TNFα, IL-6, IL-10, IFNγ and IL-1β		X		X	X	X	X	X	X	X	X
Complement profile (C3, functional assays for classical and alternative complement pathways)		X		X	X	X	X	X	X	X	X
Flow cytometry for C3 deposition on RBCs [p]	X			X	X	X	X	X	X	X	X
Ferritin, vitamin B_{12}/folate	X			X	X	X	X	X	X	X	X
Iron	X			X	X	X	X	X	X	X	X
DAT monospecific C3 and IgG	X			X	X	X	X	X	X	X	X
Immunoglobulins quantitative (IgG, IgM, and IgA) [q]	X					X			X		X
Serum cold agglutinin titer (at 4 °C) [q]	X					X			X		X
HIV, HCV-RNA, HBV-DNA	X										
EBV, *Mycoplasma pneumoniae*	X										

Table 1 Schedule of assessments: Screening to Week 24 – Part A

Study Period	**Screening [a]**		**Part A: Double-blind treatment period**								
Study Week	**-4 to -1**	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**
Study Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**
Study Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit window (± days)	**0**		**0**	**1**	**2**	**7**	**7**	**7**	**7**	**7**	**7**
MYD88 Mutation Testing (only in patients requiring a bone marrow biopsy or if already done per local institution practice)	X										
Antinuclear antibodies	X										
Serum pregnancy (B-HCG and FSH)		X									
Urine pregnancy test [r]			X			X	X	X	X	X	X
FACT-An		X		X	X	X	X	X	X	X	X
SF-12		X		X	X	X	X	X	X	X	X
EQ-5D-5L		X		X	X	X	X	X	X	X	X
Bone marrow biopsy for eligibility (as needed) [r]	X										
Adverse events		X	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X
Drug dispensation for home administration			X	X	X	X	X	X	X	X	X

Abbreviations: Ab, Antibody(ies); AE, Adverse event; B-HCG, Beta human chorionic gonadotropin; C3, Complement component 3; CAD, Cold agglutinin disease; DAT, Direct antiglobulin test; DNA, Deoxyribonucleic acid; EBV, Epstein-Barr virus; ECG, Electrocardiogram; EQ-5D-5L, EuroQol 5-Dimension 5-Level Questionnaire; FACT-An, Functional Assessment of Cancer Therapy-Anemia/Fatigue; FSH, Follicle-stimulating hormone; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; ICF, Informed consent form; IFNγ, Interferon-gamma; Ig, Immunoglobulin; IL, Interleukin; IMP, Investigational medicinal product; PEG, Polyethylene glycol; PK, Pharmacokinetic; RBC, Red blood cell; RNA, Ribonucleic acid; s.c., Subcutaneous; SF-12, 12-Item Short Form Survey; TNFα, Tumor necrosis factor-alpha; WOCBP, Women of childbearing potential.

[a] Screening period is up to 4 weeks before randomization, but certain assessments, including some laboratory assessments and quality of life questionnaires, are to be performed within 7 days before randomization.

[b] The status of vaccination against *Neisseria meningitidis* Types A, C, W, Y, and B, *Streptococcus pneumoniae*, and *Haemophilus influenzae* Type B should be confirmed and any required vaccinations or boosters are to be administered as described in Section 6.4.1.2.
[c] To receive treatment with IMP, patients who are documented nonresponders to vaccination or cannot be vaccinated prior to IMP initiation must receive prophylactic antibiotics according to local standard practices.
[d] Full physical examination will include assessment of the following items: general; head, ears, eyes, nose, and throat; dentition; thyroid (endocrine); heart; chest; lungs; abdomen; skin; extremities; back/neck; musculoskeletal system and lymph nodes.
[e] Brief physical examination will include general appearance, heart, lungs, abdomen and extremities.
[f] Both height and weight measurements should be done without shoes on. Height will be recorded at screening only.
[g] Patients will self-administer s.c. IMP, after receiving appropriate training by research personnel. IMP will be dosed at the clinical site on Day 1. Dosing diaries will be used for study treatment and are to be completed for each dose administered at the clinic or at home. On dosing days that coincide with clinic visits, doses will be administered at the clinic visit.
[h] Between site visits, patients will be instructed to report any infusion-site reaction to the investigator or other study personnel.
[i] On clinic dosing days, vital signs will be measured within 2 hours before dosing and venipuncture (and ECG, if applicable), and at 30 minutes (± 5 minutes) post dose (see Section 6.5.4.4). All vital signs will be measured after the patient has been resting in a sitting position for at least 5 minutes, except when supine or semi-reclined because of study procedures and/or AEs or if deemed necessary by the investigator.
[k] Baseline laboratory assessments within 7 days before Day 1. If IMP is administered at study visit, blood samples will be taken before dosing.
[m] PK samples will be taken 15 minutes predose at each visit.
[n] For patients with positive anti-pegcetacoplan peptide or anti-PEG Ab in last dose sample, additional samples will be collected every 6 months from last dose until Ab levels return to baseline.
[o] The use of silica reagents in coagulation panels should be avoided in all patients.
[p] If the baseline sampling is not performed at the screening visit, it will be collected at Visit 2 prior to dosing.
[q] Serum samples for immunoglobulins quantitative and CAD titer assessment to be kept at 37 ºC to 38 ºC (until serum has been removed from the clot, after which the sample can be handled at room temperature).
[r] Urine pregnancy test will be completed for WOCBP prior to dosing on days where dosing coincides with clinic visits.
[s] Bone marrow biopsy only needed if biopsy not previously undertaken within 1 year prior to ICF signature.

Note: Unscheduled additional visits may be performed at the investigator's judgment. Any of the study procedures or other assessments may be performed at the unscheduled visit at the discretion of the investigator.

Table 2 Schedule of assessments: Part B, Part C and Follow-up period

Study Period	Part B: Open-label treatment period			Part C: Open-label maintenance period					Follow-up period [p]	
									EOT/ET	EOS
Study Week	**32**	**40**	**48**	**56**	**64**	**72**	**80**	**88**	**96**	**104**
Study Day	**225**	**281**	**337**	**393**	**449**	**505**	**561**	**617**	**673**	**729**
Study Visit	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Visit window (± days)	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
RBC transfusions collection	X	X	X	X	X	X	X	X	X	X
Prophylactic antibiotic administration [a]	According to local standard practices in patients who cannot be vaccinated									
Full physical examination (including weight) [b]									X	X
Brief physical examination (including weight) [c]	X	X	X	X	X	X	X	X		
12-lead ECG (prior to venipuncture)	X								X	X
IMP administration [d]	Twice weekly----------→			Twice weekly----------→						
Infusion-site assessment [e]	X	X	X	X	X	X	X	X	X	
Concomitant medications/treatments	X	X	X	X	X	X	X	X	X	X
Vital sign measurements [f]	X	X	X	X	X	X	X	X	X	X
Urine studies	X	X	X	X	X	X	X	X	X	X
Blood [g]	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics [h]			X						X	X
Anti-pegcetacoplan peptide and anti-PEG Ab assay [i]	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation profile [k]	X	X	X	X	X	X	X	X	X	X
TNFα, IL-6, IL-10, IFNγ and IL-1β	X	X	X						X	X

Table 2 Schedule of assessments: Part B, Part C and Follow-up period

Study Period	Part B: Open-label treatment period			Part C: Open-label maintenance period					Follow-up period [p]	
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Study Week	**32**	**40**	**48**	**56**	**64**	**72**	**80**	**88**	**96**	**104**
Study Day	**225**	**281**	**337**	**393**	**449**	**505**	**561**	**617**	**673**	**729**
Study Visit	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Visit window (± days)	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Complement profile (C3, functional assays for classical and alternative complement pathways)	X	X	X						X	X
Flow cytometry for C3 deposition on RBCs [m]	X	X	X						X	X
Ferritin, vitamin B_{12}/folate	X	X	X						X	X
Iron	X	X	X						X	X
DAT monospecific C3 and IgG	X	X	X						X	X
Immunoglobulins quantitative (IgG, IgM, and IgA) [n]			X						X	X
Serum cold agglutinin titer (at 4 °C) [n]			X						X	X
Urine pregnancy test (every 4 weeks) [o]	X	X	X	X	X	X	X	X	X	X
FACT-An	X	X	X	X	X	X	X	X	X	X
SF-12	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L	X	X	X	X	X	X	X	X	X	X
Adverse events and serious adverse events	X	X	X	X	X	X	X	X	X	X
Drug dispensation for home administration	X	X	X	X	X	X	X	X		

Abbreviations: Ab, Antibody(ies); B-HCG, Beta human chorionic gonadotropin; C3, Complement component 3; CAD, Cold agglutinin disease; DAT, Direct antiglobulin test; DNA, Deoxyribonucleic acid; ECG, Electrocardiogram; EOS, End of study; EOT, End of treatment; EQ-5D-5L, EuroQol 5-Dimension 5-Level Questionnaire; ET, Early termination; FACT-An, Functional Assessment of Cancer Therapy-Anemia/Fatigue; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; IFNγ, Interferon-gamma; Ig, Immunoglobulin; IL, Interleukin; IMP, Investigational medicinal product; PEG, Polyethylene glycol; PK, Pharmacokinetic; RBC, Red blood cell; RNA, Ribonucleic acid; s.c., Subcutaneous; SF-12, 12-Item Short Form Survey; TNFα, Tumor necrosis factor-alpha; WOCBP, Women of childbearing potential.

[a] To receive treatment with IMP, patients who are documented nonresponders to vaccination or cannot be vaccinated prior to IMP initiation must receive prophylactic antibiotics according to local standard practices.

[b] Full physical examination will include assessment of the following items: general; head, ears, eyes, nose, and throat; dentition; thyroid (endocrine); heart; chest; lungs; abdomen; skin; extremities; back/neck; musculoskeletal system and lymph nodes. Weight will also be recorded at each physical examination.

[c] Brief physical examination will include general appearance, heart, lungs, abdomen and extremities. Weight will also be recorded at each physical examination.

[d] Patients will self-administer s.c. IMP, after receiving appropriate training by research personnel. Dosing diaries will be used for study treatment and are to be completed for each dose administered at the clinic or at home. On dosing days that coincide with clinic visits, doses will be administered at the clinic visit.

[e] Between site visits, patients will be instructed to report any infusion-site reaction to the study coordinator.

[f] On clinic dosing days, vital signs will be measured within 2 hours before dosing and venipuncture (and ECG, if applicable), and at 30 minutes (± 5 minutes) post dose (see Section 6.5.4.4).

[g] If IMP is administered at study visit, blood samples will be taken before dosing.

[h] PK samples will be taken 15 minutes predose at each visit.

[i] For patients with positive anti-pegcetacoplan peptide or anti-PEG Ab in last dose samples, additional samples will be collected every 6 months from last dose until Ab levels returns to baseline.

[k] The use of silica reagents in coagulation panels should be avoided in all patients.

[m] If the baseline sampling is not performed at the screening visit, it will be collected at Visit 2 prior to dosing.

[n] Serum samples for immunoglobulins quantitative and CAD titer assessment to be kept at 37 ºC to 38 ºC (until serum has been removed from the clot, after which the sample can be handled at room temperature).

[o] Urine pregnancy test will be completed for WOCBP every 4 weeks, using a home test if there is no clinic visit. Urine pregnancy test to be performed prior to dosing on days where dosing coincides with clinic visits.

[p] After completion of the maintenance period, patients will complete an EOT visit. Patients who discontinue early should complete an ET visit. An EOS visit will be performed 8 weeks (± 7 days) after treatment discontinuation for any reason.

Note: Unscheduled additional visits may be performed at the investigator's judgment. Any of the study procedures or other assessments may be performed at the unscheduled visit at the discretion of the investigator.

2 Abbreviations and definition of terms

2.1 List of abbreviations and definitions

Term	Definition
Ab	Antibodies
ACIP	Advisory Committee on Immunization Practices
ADA	Antidrug antibodies
AE	Adverse event
AIHA	Autoimmune hemolytic anemia
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ARC	Absolute reticulocyte counts
AST	Aspartate aminotransferase
AxMP	Auxiliary medicinal product
B-HCG	Beta human chorionic gonadotropin
C3	Complement component 3
CAD	Cold agglutinin disease
CDASH	Clinical data acquisition standards harmonization
CDISC	Clinical data interchange standards consortium
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CP	Classical pathway of complement
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAT	Direct antiglobulin test
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus

ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQol-5 Dimension-5 Level
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
FACT-An	Functional Assessment of Cancer Therapy–Anemia/Fatigue
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICE	Intercurrent events
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IFNγ	Interferon-gamma
IgA, IgG, IgM	Immunoglobulin A, immunoglobulin G, immunoglobulin M
IL-1β, IL-6, IL-10	Interleukin 1-beta, interleukin 6, interleukin 10
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LDH	Lactate dehydrogenase

LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mITT	Modified intent-to-treat
MMRM	Mixed-model for repeated measures
PCV13	Pneumococcal conjugate vaccine 13
PD	Pharmacodynamic
PEG	Polyethylene glycol
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
PP	Per-protocol
PPSV23	Pneumococcal polysaccharide vaccine 23
PRBCs	Packed red blood cells
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
s.c.	Subcutaneous
SOC	System organ class
SF-12	12-Item Short Form Survey
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TNFα	Tumor necrosis factor-alpha
ULN	Upper limit of normal
US	United States
WHO	World Health Organization
WOCBP	Women of childbearing potential

3 Ethics

3.1 Independent ethics committee and/or institutional review board

It is the responsibility of the investigator to obtain approval of the study protocol, possible amendments and the written patient information and ICF from the IEC/IRB. The investigator should file all correspondence with the IEC/IRB. Copies of IEC/IRB correspondence and approvals should be forwarded to Swedish Orphan Biovitrum (Sobi).

3.2 Ethical conduct of the study

This study will be conducted in compliance with this protocol, the ICH GCP [1], applicable regulatory requirements, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki [2].

3.3 Patient information and consent

It is the responsibility of the investigator to give each patient, prior to any study-related activities, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patients must be informed about their right to withdraw from the study at any time. The written patient information and/or ICF must not be changed without prior discussion with Sobi. Before any revisions are implemented, the revised written patient information and/or ICF must be approved by the IEC/IRB.

It is the responsibility of the investigator to obtain signed informed consent from all patients prior to any study-related activities. The patients should receive a copy of the written information and the signed ICF.

4 Introduction

4.1 Background

AIHA is defined as the increased destruction of RBCs in the presence of anti-RBC autoantibodies, with or without complement activation. Autoantibodies are produced by both tissue and circulating self-reactive B lymphocytes, following cooperation with T-helper lymphocytes. A third key player in anti-RBC autoimmunity is the complement system, which can induce a direct erythrocyte osmotic lysis through the sequential activation of the membrane attack complex or an extravascular hemolysis through Ab-dependent cellular cytotoxicity and phagocytosis occurring preferentially in the spleen and lymphoid organs [3].

AIHA occurs uncommonly with estimates of 1 to 3 in 100 000 population annually. The ability of the autoantibody to bind to the erythrocyte antigen at specific temperatures is fundamental to the diagnosis in terms of whether it is designated as warm (reacts maximally at 37 °C) or cold (reacts maximally at 4 °C) AIHA. The pathologic and clinical features of AIHA relate to the autoantibody class, thermal amplitude and their efficiency in activating complement [4].

AIHAs consist of warm-, cold-, and mixed-reactive Ab types that are directed against antigens on the RBC surface. The autoantibodies may be idiopathic (primary) or related to an underlying condition such as infection, malignancy, or immune disease (secondary) [5]. Cold-antibody AIHAs are further characterized into CAD, whose patients will be focused on this study.

4.1.1 Cold agglutinin disease and unmet medical need

Primary chronic CAD is an uncommon form of AIHA in which hemolysis is thought to be entirely complement-dependent. CAD accounts for about 15 % of AIHAs and is defined as an AIHA mediated by cold agglutinins, without any obvious underlying disease such as aggressive lymphoma, other overt malignancies or specific infections. Cold agglutinins are autoantibodies that can agglutinate RBCs at an optimum temperature of 3 to 4 ºC [6].

Cold antibodies (IgM) temporarily bind to the RBC membrane, which in turn activates complement, and leads to the deposition of C3b on the cell surface. These C3b-coated RBCs are cleared slowly by the macrophages of the liver through extravascular hemolysis. To a lesser extent, the complete complement cascade may be activated at the cell surface, ultimately resulting in the insertion of membrane attack complex C5b to C9 and intravascular hemolysis.

Various therapeutic approaches have been used in treating these patients, including RBC transfusions, off-label use of rituximab, rituximab-based combination therapy or bortezomib [7]. However, a substantial unmet medical need still exists.

4.1.2 Summary of clinical experience with pegcetacoplan

Clinical data from studies with pegcetacoplan in patients with PNH indicate that pegcetacoplan is an effective complement modulating agent resulting in broad control of intravascular and extravascular hemolysis.

To date, pegcetacoplan, at doses of ≤ 360 mg/day, has been well tolerated when administered via s.c. infusion, including to patients with warm AIHA and CAD (Study APL2-CP-AIHA-208 [8]; see Section 4.1.2.1).

Available safety data from completed and ongoing clinical studies have not indicated any serious safety concern in patients treated with pegcetacoplan.

Please refer to the latest version of the pegcetacoplan IB for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, PK, efficacy and safety of pegcetacoplan.

4.1.2.1 Study APL2 CP AIHA-208

This was a phase 2, open-label, prospective pilot study of pegcetacoplan conducted in subjects with a primary diagnosis of warm AIHA or CAD in parallel [8]. The study included 24 patients, 11 patients with a primary diagnosis of warm AIHA in Cohort 1 and 13 patients with a primary diagnosis of CAD in Cohort 2. Patients in each cohort were to be randomly (1:1) assigned to receive either 270 mg/day or 360 mg/day of pegcetacoplan treatment for up to 12 months (Part A, the core study phase). Seven patients in Cohort 1 (warm AIHA) and 10 patients in Cohort 2 (CAD) completed the study per the protocol.

Safety data demonstrated the tolerability of pegcetacoplan; s.c. pegcetacoplan was well tolerated in both cohorts. Most TEAEs were mild, and most (81 %) were deemed by the principal investigator to be unlikely related/unrelated to study drug. No SAEs were considered related to pegcetacoplan. The most common possibly treatment-related TEAE in Cohort 2 (CAD) was headache, reported in 3 patients (23.1 %).

Antidrug antibody responses observed in the study had no noticeable impact on the PK/PD, efficacy, or safety profile of pegcetacoplan.

This study also demonstrated that pegcetacoplan rapidly increased Hb values, an effect that persisted for 48 weeks. This result was more prominent in patients with CAD (Cohort 2). In addition, transfusion avoidance during the 12 months of the core study phase was observed in Cohort 2 in 77 % of patients after treatment with pegcetacoplan. Improvements in hemolysis by reduction in ARCs, LDH and indirect bilirubin were observed in both cohorts.

Persistent inhibition of the alternative complement pathway was demonstrated without affecting classical complement activation. Increases in C3 levels were also observed in both dosage groups (270 mg/day and 360 mg/day). There was also a trend of reduction of C3 deposition on RBCs (% Type I) in both cohorts, which suggests that pegcetacoplan protects RBCs from complement-mediated attack.

Serum pegcetacoplan concentrations reached steady state between Week 4 and Week 8. After reaching steady state, mean trough concentrations of pegcetacoplan were generally higher in the 360 mg/day group, supporting that exposure increased in a dosage-dependent manner.

In summary, pegcetacoplan produced consistent, meaningful, and prolonged effects on most relevant clinical efficacy measures along with an acceptable safety profile in patients with warm AIHA and CAD.

4.2 Study rationale

Aberrant complement pathway activation has been demonstrated in many autoimmune disorders, particularly in diseases associated with pathogenic autoantibodies [9]. Binding of C1 complex, the triggering mechanism of the CP, to an immune complex containing a self-antigen and an autoantibody results in the formation of the CP C3 convertase, C4b2a. Subsequent cleavage of

complement proteins C3 and C5 results in generation of C3a and C5a, anaphylatoxins that attract and activate effector immune cells to the site of Ab binding/complement activation; deposition of C3 opsonins that mediate phagocytosis and lymphocyte activation and, finally, the formation of the membrane attack complex, a lytic pore that disrupts the cellular membrane and leads to cellular destruction [10]. Thus, complement components have long been an attractive target for drug development.

Pegcetacoplan, the active ingredient in pegcetacoplan solution for s.c. infusion 1080 mg/20 mL, is a pentadecapeptide (a bioactive cyclic tridecapeptide C3-inhibiting moiety and a 2-amino acid linker) covalently coupled to each end of a linear 40-kDa PEG chain, so that there are 2 active peptide moieties per molecule of pegcetacoplan. The peptide portion of the drug binds to complement C3 and is a broad modulator of the complement cascade, a biological process that is part of innate immunity and is involved in multiple inflammatory processes. The PEGylation of the molecule imparts slower elimination from mammalian systems following administration (see the pegcetacoplan IB).

On the basis of scientific and clinical evidence on the role of complement activation in CAD, it can be concluded that pegcetacoplan, which acts through modulation of the complement system, has the potential to prevent C3-mediated extravascular and intravascular hemolysis in CAD patients.

Pegcetacoplan was able to rapidly increase Hb values in 10 patients with CAD treated in the phase 2 APL2 CP AIHA-208 study, reducing both intravascular and extravascular hemolysis (as shown by reduction and normalization of LDH, indirect bilirubin and ARCs) and leading to transfusion independency in the majority of them, being well tolerated.

Thus, this phase 3 study is being conducted to confirm the safety and efficacy of pegcetacoplan in patients with CAD.

Pegcetacoplan will be compared to placebo in a double-blinded, randomized fashion. The treatment duration will be 24 weeks for both treatment groups to ensure capturing a durable treatment effect. At the end of the randomized portion of the study, all enrolled patients will be offered a 24-week treatment with pegcetacoplan in an open-label fashion, and 48 additional weeks to allow treatment continuity until the product is commercially available.

4.3 Potential risks and benefits

Cumulatively, up to 10 July 2021, 342 subjects have been systematically exposed (via intravenous and s.c. route) to pegcetacoplan in completed and ongoing studies across multiple indications. The administration of pegcetacoplan was well tolerated and the safety data did not indicate any significant safety concern. Nonetheless, a number of safety monitoring practices are being employed by this protocol to ensure patient safety, including physical examination, vital signs monitoring, ECGs, hematology (including coagulation), serum chemistry, urinalysis and prompt reporting of AEs.

As with other complement-inhibiting drugs, there is a potential increased risk of infections with encapsulated pathogens including *Streptococcus pneumoniae*, *Neisseria meningitidis* (serogroups A, C, W, Y, and B), and *Haemophilus influenzae* Type B. There have been no reports of meningococcal infection or other severe infections potentially related to encapsulated bacteria through 334.5 person-years of systemic pegcetacoplan exposure. The serious infections that were observed across studies were manageable and did not require discontinuation from pegcetacoplan. Therefore, the sponsor believes that the data do not support an increased risk of serious infections attributable to pegcetacoplan treatment.

Thus, patients will be required to have documented evidence of vaccination against these pathogens within 2 years before study initiation, or will be required to receive vaccination upon initiation of IMP.

To receive treatment with IMP, patients who are documented nonresponders to vaccination or cannot be vaccinated prior to IMP initiation must receive prophylactic antibiotics according to the local standard practices.

Body temperature and other vital signs will be monitored at all clinic visits, and relevant blood parameters will be monitored throughout the study to assess for signs of infection. Patients will be provided with emergency study cards that list symptoms associated with infections caused by encapsulated organisms. This study card also guides patients with instructions to contact their study physician or seek emergency medical care in the event they experience any of the listed symptoms. In the event of a suspected infection, the principal investigator should provide guidance on appropriate action to be taken.

Infusion-site/pump safety will be assessed during clinical visits, and any significant finding from the assessment will be reported as an AE (see Section 6.5.4.1).

Hemolysis occurring in study subjects after sudden pegcetacoplan withdrawal has been observed in 2 patients with PNH. Abrupt discontinuation of pegcetacoplan treatment may render PNH red blood cells unprotected against complement activation, potentially resulting in hemolysis leading to severe anemia.

Whenever possible, the study medical monitor will be contacted before interrupting or discontinuing treatment with IMP.

4.3.1 COVID-19 risk mitigation measures

The sponsor is not currently aware of any evidence associating pegcetacoplan use with specific risks or complications of COVID-19. The sponsor recognizes the need to consider the public health risks of the COVID-19 pandemic within the context of conducting a clinical study. Because these risks may change as the pandemic evolves and may vary on the basis of geographic location, the sponsor will continue to evaluate the risk/benefit around study conduct on an ongoing and patient-by-patient basis.

In the event that an investigative site is closed or a patient is unable/unwilling to attend a study visit because of COVID-19 restrictions and, in the opinion of the investigator, it is in the patient's best interest to continue in the study, the following mitigation measures may be implemented for the study and utilized if deemed necessary and authorized by the sponsor, including but not limited to:

- In locations where home nursing services may be utilized, a home nursing vendor may be set up to complete assessments at a patient's home.
- Collection of AEs or SAEs should be done over the phone and documented in the source documents and in the correct eCRF page.
- If a patient has been tested for COVID-19, the results, if available, will be documented in the eCRF.
- Minimized schedule of assessment can be followed during COVID-19 restrictions (Table 5 and Table 6), including the use of certified local laboratory.
- The EDC system will capture any missed assessments related to COVID-19.
- Where applicable, relevant study documentation will be updated and communicated to Health Authorities and/or IRBs/IECs as required.

COVID-19 vaccination is permitted during the course of the study as per local standard of care. Details of the deployed vaccine should be recorded in the medical notes and study visits should continue as planned if possible and appropriate.

5 Study objectives and endpoints

5.1 Primary objective

The primary objective of this study is to demonstrate the efficacy of twice-weekly s.c. 1080-mg infusions of pegcetacoplan compared with that of placebo in patients with CAD.

5.1.1 Primary endpoint

The primary efficacy endpoint is response to treatment at Week 24.

Response is defined as:

- An increase in Hb of ≥ 1.5 g/dL from Baseline or Hb normalization at Week 16; AND
- Maintenance of this effect from Week 16 to Week 24 AND
- The absence of PRBC transfusions (between Week 5 and Week 24).

Note: Hb normalization is defined as within normal range (between the defined ULN and LLN), as set by the testing laboratory.

5.2 Secondary objectives

The following are the key secondary objectives of this study:

- To demonstrate the effect of pegcetacoplan on the number of PRBC transfusions in patients with CAD.
- To demonstrate the effect of pegcetacoplan on health-related quality of life in patients with CAD.

The following are the other secondary objectives of this study:

- To assess the effect of pegcetacoplan on clinical laboratory markers of hemolysis and transfusion dependence in patients with CAD.
- To determine the durability of response in patients with CAD receiving pegcetacoplan.
- To assess tolerability, safety and immunogenicity of pegcetacoplan in patients with CAD.
- To describe long-term effect of pegcetacoplan in patients with CAD.

5.2.1 Secondary endpoints supporting the secondary objectives

5.2.1.1 Key secondary efficacy endpoints

The following are the key secondary endpoints for this study:

- Change from Baseline to Week 24 in Hb level.
- Transfusion avoidance (Yes/No) from Week 5 to Week 24.
- Change from Baseline to Week 24 in the FACT-An score.

5.2.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints are as follows:

Part A:

- Number of PRBC transfusions from Week 5 to Week 24.
- Change from Baseline to Week 24 in the following:
    - LDH level.
    - Haptoglobin level.
    - Indirect bilirubin level.
    - ARC.
    - D-dimer level.
- Normalization of markers of hemolysis at Week 24, specifically:
    - LDH level.
    - Indirect bilirubin level.
    - ARC.

- Time to first normalization from Baseline to Week 24 for the following:
  - Hb level.
  - LDH level.
  - Indirect bilirubin level.
  - ARC.
- Number of PRBC units transfused from Week 5 to Week 24.
- Change from Baseline to Week 24 in the following:
  - FACIT-F subscale score of the FACT-An scale.
  - SF-12 score.
  - EQ-5D-5L score.

Part B:

- Change from Baseline to Week 48 in the following:
  - Hb level.
  - LDH level.
  - Haptoglobin level.
  - Indirect bilirubin level.
  - ARC.
  - D-dimer level.
- Normalization of markers of hemolysis at Week 48, specifically:
  - LDH level.
  - Indirect bilirubin level.
  - ARC.
- Durability of response for patients randomized to pegcetacoplan who achieve the primary endpoint at Week 24.
- Change from Baseline to Week 48 in the following:
  - FACT-An score.
  - FACIT-F subscale score of the FACT-An scale.
  - SF-12 score.
  - EQ-5D-5L score.

5.2.1.3 Tertiary efficacy endpoints

The tertiary efficacy endpoints are as follows:

Part C:

- Change from Baseline to Week 96 in the following:
  - Hb level.
  - LDH level.
  - Haptoglobin level.
  - Indirect bilirubin level.
  - ARC.

  - D-dimer level.
- Normalization of markers of hemolysis at Week 96, specifically:
  - LDH level.
  - Indirect bilirubin level.
  - ARC.
- Change from Baseline to Week 96 in the following:
  - FACT-An score.
  - FACIT-F subscale score of the FACT-An scale.
  - SF-12 score.
  - EQ-5D-5L score.

5.2.1.4 Safety endpoints

The safety endpoints are as follows:

- AEs up to 8 weeks after EOT.
- SAEs up to 8 weeks after EOT.
- AEs leading to premature discontinuation of IMP.
- Clinically meaningful laboratory abnormalities up to 8 weeks after EOT.
- Changes from Baseline in laboratory parameters markers (Baseline will be taken as the last measurement prior to the first dose of IMP).
- Clinically meaningful ECG abnormalities up to 8 weeks after EOT.
- Clinically meaningful changes in vital signs from Baseline up to 8 weeks after EOT.
- Immunogenicity: presence of Ab to polyethylene glycol and pegcetacoplan peptide throughout treatment and follow-up periods.

5.3 Exploratory objectives

- To evaluate the PK of pegcetacoplan following twice-weekly s.c. infusions.
- To evaluate the effect of pegcetacoplan in complement biomarkers.

5.3.1 Exploratory endpoints

The exploratory endpoints are as follows:

- Pegcetacoplan PK concentrations at Week 24 and Week 48.
- Changes from Baseline to Week 24 and Week 48 in complement biomarkers (C3 levels, functional assays for classical and alternative complement pathways).
- Changes from Baseline through Week 24 and Week 48 in C3 deposition on RBCs by flow cytometry.
- Changes from Baseline to Week 24 and Week 48 in inflammatory biomarkers: TNFα, IL-6, IL-10, IFNγ and IL-1β.

- Normalization of haptoglobin level at Week 24, Week 48 and Week 96.
- Time to first normalization from Baseline to Week 24 for haptoglobin level.

6 Investigational plan

6.1 Overall study design and plan

This is a phase 3, randomized, double-blind, placebo-controlled multicenter study of pegcetacoplan (1080 mg) or placebo, administered twice weekly by s.c. infusion in patients with CAD.

A total of 57 patients with CAD will be enrolled in this study. Patients will be randomized in a ratio of 2:1 to receive either pegcetacoplan or placebo, respectively. The randomization will be stratified by transfusion history (number of transfusions during the 6-month period prior to randomization ≥ 1; 0). Every effort should be made to enroll patients in both subgroups.

The planned length of participation in the study for each patient is a maximum of 104 weeks. This study will consist of 5 periods:

- Screening period: up to 4 weeks.
- Double-blind treatment period: 24 weeks (Part A).
- Open-label treatment period: 24 weeks (Part B).
- Open-label maintenance period: up to additional 48 weeks or until the product becomes commercially available (Part C).
- Follow-up period: 8 weeks.

The study design is outlined in Figure 1, and the visit schedule and planned assessments at each visit are detailed in Table 1 and Table 2.

No formal interim analyses are planned. However, data will be reported for Part A (double-blind treatment period) once all patients have completed their Week 24 visit (or have early discontinued) and the database has been cleaned and verified for all visits up to and including Week 24. Similarly, data will be reported after Part B (see Section 8.3.7).

6.1.1 Screening period (up to 4 weeks)

Informed consent will be obtained during a screening visit prior to any study-related procedures being conducted. Some screening assessments, including laboratory tests and quality of life questionnaires, will be performed within 7 days before randomization. Patients will be screened to confirm that entrance criteria for the study have been met. Key inclusion and exclusion criteria will be reviewed by the study medical monitor and eligibility will be confirmed prior to the enrollment. Patients experiencing acute hemolytic crisis may receive blood cell transfusions

during the screening period. For Hb level qualification, the latest post-transfusion value will be used as Baseline, and the threshold of ≤ 9.0 g/dL must be met.

6.1.1.1 Retesting and rescreening

Patients who fail to qualify for the study on the basis of certain laboratory parameters may be retested and/or rescreened at the discretion of the investigator.

6.1.1.1.1 Retesting

Retesting is defined as repeating laboratory tests within the same screening period.

Patients who initially fail to qualify for the study on the basis of laboratory test results not meeting inclusion criteria or due to technical issues (e.g., hemolysis, clotting) may have, at the discretion of the investigator, any individual laboratory parameter retested 1 time within the 4-week screening period. Retesting within the 4-week screening period does not constitute rescreening; however, if retesting falls outside of the 4-week screening period, it should be considered rescreening (see below).

In case of retesting for Hb level qualification, the last measured value will be used as Baseline.

6.1.1.1.2 Rescreening

Rescreening is permitted for patients who consent to participate in the study but who do not initially meet all the requirements as outlined in the inclusion and exclusion criteria. In this case, additional screening visits and/or repeat screening assessments may be conducted, as needed, to establish eligibility.

Screening is limited to 3 attempts (screening and 2 additional rescreening attempts).

In the event that rescreening occurs and the patient has not remained in the screening period, the individual is required to reconsent and must be assigned a new identification number.

6.1.1.2 Screen failures

Screen failures are defined as patients who consent to participate in the clinical study but who do not meet 1 or more criterion required for participation and are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography and reason for screen failure.

6.1.2 Double-blind treatment period (24 weeks): Part A

A total of 57 patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 2:1 ratio to receive either pegcetacoplan or placebo.

Patients randomized into the study will receive IMP (pegcetacoplan or placebo) twice weekly for 24 weeks.

All standard-of-care medications can be continued, with the exception of protocol-defined prohibited medications (see Section 6.4.10.2).

During the double-blind treatment period, patients will receive a blood transfusion if their Hb level is ever shown to be < 7.0 g/dL. During this study period, transfusions will be considered, at the investigator's discretion, in symptomatic patients with Hb levels ≥ 7.0 and < 9.0 g/dL.

6.1.3 Open-label treatment period (24 weeks): Part B

All patients who complete the 24-week double-blind treatment period will be eligible to enter the open-label treatment period, in which they will receive pegcetacoplan 1080 mg twice weekly for up to 24 weeks (Week 48).

6.1.4 Open-label maintenance period (up to additional 48 weeks or until the product becomes commercially available): Part C

After completion of the open-label treatment period, patients who benefit from therapy without significant side effects will continue receiving pegcetacoplan 1080 mg s.c. twice weekly for a maximum of 48 additional weeks or until the product is commercially available.

At the end of the study, the sponsor will inform the investigators of the appropriate course of action based on the study results.

6.1.5 Follow-up period (8 weeks)

After completion of the open-label maintenance period, or if patients discontinue pegcetacoplan treatment early, an EOT visit will be performed, followed by an EOS visit 8 weeks later. See Figure 1 for the study schematic illustrating the study periods as a function of time.

6.1.6 Unscheduled visits

Unscheduled additional visits may be performed at the investigator's judgment. Any of the study procedures or other assessments may be performed at the unscheduled visit at the discretion of the investigator.

6.2 Discussion of study design, including the choice of control groups

In this double-blinded, randomized, phase 3 study, patients will be randomized in a ratio of 2:1 to receive pegcetacoplan or placebo. The study will enroll patients affected by CAD who have an

Hb level ≤ 9 g/dL. There are no currently approved therapies for patients with CAD in need of treatment; therefore, the choice of placebo as comparator is fully justified.

The primary endpoint of the study is a composite endpoint aimed at demonstrating a significant effect of pegcetacoplan on hemoglobin levels that is durable and effective in reducing transfusion requirement.

The treatment duration will be 24 weeks for both treatment groups to ensure capturing a durable treatment effect, with an extended 24-week open-label treatment period offered to all patients enrolled in the study, and 48 additional weeks to allow treatment continuity until the product is commercially available.

Those patients randomized to the placebo group requiring a rescue blood transfusion according to the study-specified criteria for transfusion or those who receive a prohibited concomitant medication during the treatment period will be considered as nonresponders.

6.3 Selection of study population

6.3.1 Inclusion criteria

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

1. Age 18 years or older.
2. Diagnosis of primary CAD on the basis of the presence of **all** the following criteria:
    a. Signs of hemolysis with abnormal values for at least 2 of the following hemolytic markers:
        i. Reduced haptoglobin level (< LLN).
        ii. Elevated LDH level (> ULN).
        iii. Elevated indirect bilirubin level (> ULN; > 3 x ULN for patients with Gilbert-Meulengracht syndrome).
        iv. Increased ARC (above the ULN).
    b. Monospecific direct antiglobulin test strongly positive for C3d.
    c. Cold agglutinin titer ≥ 64 at 4 °C.
3. Hb level ≤ 9 g/dL.
4. An absolute neutrophil count ≥ 1500 cells/mm^3 at screening.
5. Documented results from bone marrow biopsy within 1 year of screening with lymphoproliferative infiltration ≤ 20 %. Patients who have not received a bone marrow biopsy within 1 year of their screening visit or for whom bone marrow biopsy reports are

incomplete or unavailable will be required to receive a bone marrow biopsy to determine eligibility.

6. Body weight ≤ 100 kg.
7. Either have vaccination against *S. pneumoniae*, *N. meningitidis* (Types A, C, W, Y, and B), and *H. influenzae* (Type B) within 2 years prior to screening or agree to receive vaccination during screening as follows:
   - First dose of vaccine against *N. meningitidis* Types A, C, W, and Y at least 2 weeks prior to start of study drug with second dose 2 months later (Study Day 57), and then boosters every 5 years.
   - First dose of the vaccine against *N. meningitidis* Type B at least 2 weeks prior to start of study drug with a second dose after at least 1 month (Study Day 29). First booster dose 1 year later, and then additional booster doses every 2 to 3 years.
   - *S. pneumoniae*: PCV13 and/or PPSV23 as per ACIP guidelines for adults or children with immunocompromising conditions.
   - *H. influenzae* Type B: 1 dose at least 2 weeks prior to start of study drug.

   Vaccination is mandatory unless documented evidence exists that patients are nonresponders to vaccination. Patients who were not previously vaccinated should not receive multiple vaccines on the same day.
8. WOCBP, defined as any women who have experienced menarche and who are NOT permanently sterile or postmenopausal, must have a negative pregnancy test at screening and agree to use protocol-defined methods of contraception for the duration of the study and 8 weeks after their last IMP dose.

   Note: Postmenopausal is defined as having had 12 consecutive months with no menses without an alternative medical cause.
9. Men must agree to the following for the duration of the study and 8 weeks after their last IMP dose:
   a. Avoid fathering a child.
   b. Use protocol-defined methods of contraception.
   c. Refrain from donating sperm.
10. Willing and able to give written informed consent.

6.3.2 Exclusion criteria

The presence of any of the following will exclude a patient from inclusion in the study:

1. Have received other anticomplement therapies (approved or investigational) within 5 half-lives of the agent prior to randomization (e.g., eculizumab within 10 weeks,

ravulizumab within 36 weeks or sutimlimab within 4 weeks) and are not able or willing to refrain from using them during the study.

2. Treatment with rituximab monotherapy within 12 weeks prior to randomization, or rituximab combination therapies (e.g., with bendamustine, fludarabine, other cytotoxic drugs or ibrutinib) within 16 weeks prior to randomization.
3. Use of prohibited medications as described in Section 6.4.10.2. Refer to Section 6.4.10.1 for the list of acceptable medications and required stable regimen periods for each.
4. Diagnosis of systemic lupus erythematosus or other autoimmune disease with antinuclear antibodies.
5. History of an aggressive lymphoma or presence of a lymphoma requiring therapy.
6. Have received an organ transplant.
7. Cold agglutinin syndrome secondary to *Mycoplasma pneumoniae*, Epstein-Barr virus or other specific causative infection.
8. HIV or hepatitis C virus detectable by polymerase chain reaction at screening or documented in the patient's medical record.
9. Chronic inactive hepatitis B virus with viral loads > 1000 IU/mL (> 5000 copies/mL) at screening or documented in the patient's medical record. Eligible patients who are chronic active carriers (≤ 1000 IU/mL) must receive prophylactic antiviral treatment (e.g., entecavir, tenofovir, lamivudine) according to local country guidelines.
10. Presence of an active malignant disease within the last 12 months other than skin basal cell carcinoma or in situ carcinoma of the cervix. A low-grade lymphoproliferative bone marrow disorder not requiring therapy by itself is not defined as a malignant disease in this context.
11. A monospecific direct antiglobulin test result of IgG > 1+.
12. Presence or suspicion of liver dysfunction as indicated by elevated ALT > 2.5 x ULN, or direct bilirubin levels > 2 x ULN.
13. Hypersensitivity to pegcetacoplan or to any of the excipients or placebo compounds.
14. Known or suspected hereditary fructose intolerance.
15. Unresolved infection caused by encapsulated bacteria including *N. meningitidis*, *S. pneumoniae* and *H. influenzae.*
16. Presence or suspicion of severe recurrent or chronic infections that, in the opinion of the investigator, increase the patient's risk by participating in the study.
17. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days prior to screening period.

18. If breastfeeding, is unwilling to discontinue for the duration of study and for at least 8 weeks after the final IMP dose.
19. Inability to cooperate with study procedures.
20. Any disease(s), psychiatric condition, metabolic dysfunction, or findings from a physical examination or clinical laboratory test result that would cause reasonable suspicion of a disease or condition that may jeopardize the patient's wellbeing, that may increase the risk associated with study participation, that may affect the interpretation of the results, or that would make the patient unsuitable for this study.
21. Protected adults (guardianship, trusteeship) who are unable to express their consent and persons under court protection.

6.3.3 Withdrawal of patients from treatment or study

6.3.3.1 Withdrawal from treatment

A patient should be withdrawn from the study treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient. Specific treatment stopping criteria are provided in Section 6.4.7.

When a patient is withdrawn from treatment, the study site must immediately notify the study medical monitor, and the date of last IMP dose and the date and reason for treatment withdrawal should be clearly described in the relevant sections of the eCRF. If a patient is removed from treatment because of an AE, the reason for treatment withdrawal should always be stated as 'adverse event' irrespective of whether this was the investigator's or the patient's decision.

The patient will continue to participate in the study without taking study treatment. Patients who stop study treatment prior to the exit visit should undergo all follow-up visits and procedures through study completion, unless they are unwilling or unable or consent has been withdrawn. Patients who wish to fully withdraw from the study before completion should be encouraged to complete the Early termination visit (see Table 2).

6.3.3.2 Withdrawal from study

A patient may withdraw from the study at any time at his/her own request or at the request of their legally authorized representative, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Whenever possible and irrespective of the reason for withdrawal, the patient should be examined as soon as possible. Relevant samples should be obtained and all relevant assessments should be completed. The eCRF should be completed as far as possible. Date and reason for the study withdrawal should be clearly described in the eCRF.

Once a patient leaves the study, he/she may not reenter the study.

6.3.3.3 Lost to follow-up

A minimum of 3 documented attempts must be made to contact any patient lost to follow-up at any point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the patient's last known address via courier or mail (with an acknowledgment of receipt request) asking that the patient return to the site for final safety evaluations and to return any IMP.

Should the patient continue to be unreachable, they will be considered to have withdrawn from the study.

6.3.4 Replacement of withdrawn patients

Withdrawn patients will not be replaced.

6.3.5 Specific restrictions/requirements

6.3.5.1 Acceptable methods of contraception

Acceptable methods of contraception include:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral, intravaginal or transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral, injectable or implantable.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner (provided that the partner is the sole sexual partner of the WOCBP study patient and the vasectomized partner has received medical assessment of the surgical success).
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments).
- Male condom, with or without spermicide (for male study patients with female partners of childbearing potential only).

Not all methods of contraception may be available in all of the countries in which the study is being conducted.

Note: Sexual abstinence is accepted only when it is the preferred and usual lifestyle of the patient.

Patients must agree to use an acceptable method of contraception during the study and for 8 weeks after their last dose of IMP.

Male patients will be counseled to avoid donating semen during the time between the first screening and the final exit visit and for the 8 weeks after their last dose of IMP.

6.3.5.2 Vaccination and preventive antibiotic requirements

Details about required vaccination against *N. meningitidis* (Types A, C, W, Y, and B), *S. pneumoniae* (with a PCV13 or PPSV23 vaccine), and *H. influenzae* Type B (Hib) and required/recommended preventive antibiotics are provided in Section 6.4.1.2.

6.3.6 Study stopping criteria

The study enrollment will be suspended if:

- 2 patients from 2 different investigational sites experience a Grade 4 AE assessed as related to the IMP by the investigator.
- 1 patient experiences a Grade 5 AE assessed as related to the IMP by the investigator.

The sponsor will thoroughly evaluate the reported adverse reactions and will resume the study only if an alternative explanation of the reported events is identified. In case the decision to stop the study is made, the sponsor will communicate the appropriate action for enrolled patients who are on treatment with the active drug based on the risk-benefit assessment. The sponsor or designee will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action, when applicable. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC.

6.4 Treatments

6.4.1 Treatments administered

6.4.1.1 Investigational medicinal products

Table 3 Investigational medicinal products

Investigational product	Dosage form	Route	Dose	Dosage regimen
Pegcetacoplan	Sterile solution in stoppered glass vials	Subcutaneous	1080 mg	Twice weekly
Placebo	Sterile solution in stoppered glass vials	Subcutaneous	Not applicable	Twice weekly

The pegcetacoplan treatment group will receive a dosage of 1080 mg twice weekly via s.c. infusion (20 mL) during the double-blind treatment period (24 weeks).

The placebo group will receive placebo s.c. infusion twice weekly during the double-blind treatment period.

Following the double-blind treatment period, patients from both treatment groups may enter the open-label treatment period (24 weeks) and will receive pegcetacoplan 1080 mg twice weekly via s.c. infusion (20 mL) (equivalent to 308 mg/day).

The open-label treatment period will be followed by an open-label maintenance period (maximum of additional 48 weeks or until the product becomes commercially available), and patients who benefited from therapy without significant side effects during the double-blind treatment period will continue receiving pegcetacoplan 1080 mg twice weekly via s.c. infusion (20 mL).

6.4.1.2 Vaccination and preventive antibiotics

6.4.1.2.1 Vaccination

To receive treatment with IMP, patients will be required to be vaccinated as per ACIP recommendations for adults or children with complement deficiencies and/or immunocompromising conditions (available at https://www.cdc.gov/vaccines/schedules/hcp/index.html) as follows:

Patients previously vaccinated will have documented evidence of vaccination against the following within 2 years of screening: *N. meningitidis* Types A, C, W, Y, and B (administered as 2 separate vaccinations), *S. pneumoniae* (with a PCV13 or PPSV23 vaccine), and *H. influenzae* Type B (Hib) vaccine (see Section 6.3.1, Inclusion Criterion #7).

Patients not previously vaccinated will have to receive vaccines during screening as follows:

- First dose of vaccine against *N. meningitidis* Types A, C, W, and Y at least 2 weeks prior to start of study drug with second dose 2 months later (study Day 57), and then boosters every 5 years.
- First dose of the vaccine against *N. meningitidis* Type B at least 2 weeks prior to start of study drug with a second dose after at least 1 month (study Day 29). First booster dose 1 year later, and then additional booster doses every 2 to 3 years.
- *S. pneumoniae*: PCV13 and/or PPSV23 as per ACIP guidelines for adults or children with immunocompromising conditions.
- *H. influenzae* Type B: 1 dose at least 2 weeks prior to start of study drug.

Vaccination is mandatory, unless documented evidence exists that patients are nonresponders to vaccination. The investigator will discuss with the sponsor regarding individual patient circumstances. Patients who were not previously vaccinated should not receive multiple vaccines on the same day.

Vaccines will be sourced locally by the study sites and reimbursed by the sponsor, or sourced by the sponsor if local sourcing is not feasible.

An AxMP is a medicinal product used for the needs of a clinical study as described in the protocol, but not as an IMP. In this study, the described mandatory vaccines are considered as AxMP and safety reporting applies for them, see Sections 6.5.4.1.3.1 and 6.5.4.1.4.1.

6.4.1.2.2 Preventive antibiotics

To receive treatment with IMP, patients who are documented nonresponders to vaccination or cannot be vaccinated prior to IMP initiation must receive prophylactic antibiotics according to local standard practices.

6.4.2 Identity of investigational medicinal products

The IMP is pegcetacoplan, which will be provided as a sterile solution of pegcetacoplan at 54 mg/mL (1080 mg/20 mL) in 10 mM acetate buffer, pH 5.0, containing 4.1 % sorbitol, provided in single-use stoppered glass vials. Additional information is provided in the pegcetacoplan IB.

Placebo will be provided as a sterile solution of 10 mM sodium acetate, pH 5.0, containing 4.1 % sorbitol supplied in stoppered glass vials.

Possible deficiencies related to the handling and quality of the IMP(s) should be reported to the study medical monitor and also directly to complaints@sobi.com.

6.4.2.1 IMP packaging and labeling

The IMP is supplied in 20-cc glass vials. Please refer to the pharmacy manual for details.

All IMP will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

Changes to sponsor-supplied packaging prior to administration may not occur without full agreement, in advance, by the sponsor.

6.4.2.2 IMP storage and handling

The IMP should be stored refrigerated at 2 °C to 8 °C, both at home and in the clinic. Temperature monitoring is required at the investigator site (or documented storage location) to ensure that the IMP is maintained within an established temperature range.

The investigator or appropriately qualified site staff will be responsible for the following activities:

- Ensuring that the IMP is stored in a secure, limited-access location at the site.
- Ensuring that the temperature is monitored throughout the duration of the study and that records are maintained.

Limited responsibility may be delegated to the pharmacy or to another member of the study team, but this delegation must be documented.

A pharmacist or appropriately qualified designated person will be responsible for the following:

- Storing the IMP appropriately.
- Dispensing the IMP vials to the patient and entering the unique subject identifier as appropriate.

When the patient receives the IMP from the site, it should be transported in a sponsor-approved bag or box containing previously temperature-conditioned cold plates to ensure that the storage temperature (2 °C to 8 °C) is maintained. Temperature monitoring will not be required during transport or at the patient's residence. It is required for the patient to complete the diary, confirming that all IMP was kept refrigerated at 2°C to 8°C (35.6°F to 46.4°F) prior to removing from refrigerator for use.

6.4.3 Method of assigning patients to treatment groups

Randomization will occur through the IRT system.

All patients who meet all the inclusion criteria and none of the exclusion criteria will be enrolled in the study after eligibility review the study medical monitor, until such time that 57 patients have been enrolled in the study. Patients will then be randomly assigned through the IRT system to either pegcetacoplan or placebo in a 2:1 ratio. The randomization will be stratified according to number of transfusions during the 6-month period prior to randomization ≥ 1; 0. Every effort should be made to enroll patients in both subgroups.

Blinded IMP supplies labeled with kit numbers and other information as per Master Label and in line with regulatory requirements will be provided to each study site. IMP dosing will be initiated at the site after randomization. At each visit when IMP is administered and dispensed, the study staff will contact the IRT to obtain appropriate kit numbers.

For the open-label treatment and maintenance periods, all patients will receive pegcetacoplan open-label.

Please refer to the study manuals for further details of randomization and unblinding.

6.4.4 Selection of doses

A twice-weekly dose of 1080 mg was selected as the dosing regimen on the basis of PK modeling, which predicts a pegcetacoplan serum level for this regimen between those observed for the 270-mg and 360-mg daily dose regimens. The pegcetacoplan serum concentration predicted for 1080-mg twice-weekly s.c. administration was confirmed in a study of healthy subjects (e.g., Study 101; refer to the pegcetacoplan IB).

Population PK modeling based on pooled data from 10 clinical studies, including data up to Week 16 from Study APL2-302, confirmed that the pegcetacoplan exposure achieved at a dosage of 1080 mg s.c. twice weekly is intermediate to those predicted for dosages of 270 mg and 360 mg s.c. once daily (refer to the pegcetacoplan IB).

The exposure-response model for Hb provides support for the hypothesis that the phase 3 dose regimen of 1080 mg twice weekly will be effective in increasing Hb levels to normal or near-normal levels. Indeed, steady-state pegcetacoplan serum concentrations are expected to reach 99 % of the maximal predicted Hb response. Similarly, the exposure-response model for LDH also provides support for the hypothesis that the phase 3 dose regimen of 1080 mg twice weekly will be an effective dosage for LDH response. Steady-state pegcetacoplan serum concentrations are expected to reach 95 % of the maximal predicted LDH response.

6.4.5 Selection and timing of doses for each patient

Patients will self-administer s.c. IMP, after receiving appropriate training by research personnel. IMP will be dosed at the clinical site on Day 1. On dosing days that coincide with clinic visits, doses will be administered at the clinic visit.

Patients will be instructed to self-administer their IMP only as prescribed and to contact the investigator immediately for guidance in the event of any missed doses.

Dosing diaries will be used for study treatment and are to be completed for each dose administered at the clinic or at home. Patients should not deviate from the IMP dosing schedule: Day 1 and Day 4 of each treatment week (e.g., Monday/Thursday/Monday/Thursday).

The preferred site of infusion will be the abdomen. If administration into the abdomen is not feasible, alternative appropriate sites are acceptable (see the Pump Instructions for Use document for more details).

The typical s.c. infusion time for pegcetacoplan is approximately 30 minutes if using 2 sites, or approximately 60 minutes if using 1 site.

During initial qualification, the research nurse or other appropriately qualified and trained research personnel will administer the s.c. infusions (as needed) and will qualify and supervise the self-administration or caregiver administration. These qualified research personnel will be made available for a minimum of 2 doses to ensure the patient has been qualified to conduct self-administration; the duration can be shortened if qualification happens sooner. During qualification, the patient or caregiver must demonstrate to the research personnel their ability to safely and effectively administer the IMP using the infusion pump. Following self-administration or caregiver administration qualification, patients or caregivers may self-administer the s.c. infusions without supervision. Once qualified, the patient or caregiver will continue to administer infusions at the clinic on those days when a clinic visit occurs and at an off-site location convenient to the patient on all other days. Self-administration or caregiver

administration conducted at the clinic will be supervised to ensure that the patient or caregiver continues to remain compliant with the administration guidelines.

Missed doses will be handled on a case-by-case basis between the investigator and the study medical monitor, with the general approach being to administer a missed dose as soon as noticed, unless the next dose has already been administered.

NOTE: If the patient or caregiver requires further training, the self-administration qualification period may be extended as necessary. Caregiver administration may be conducted by a member of the patient's household, a family member, etc, who will undergo the same qualification criteria (qualification is not intended to be restricted to the patient).

6.4.6 Dose modification

Any dose modification (treatment interruption/discontinuation) necessary to manage AEs should be discussed with the study medical monitor.

6.4.7 Treatment stopping criteria

Pegcetacoplan will be discontinued in an individual patient if any of the following laboratory abnormalities and/or AEs are observed that are assessed as causally related to the IMP (i.e., no alternative explanation is identified) by the investigator:

- Any Grade ≥ 3 nonhematological laboratory abnormality (other than Grade 3 hypoglycemia; Grade 3 AST, GGT, and total bilirubin caused by unconjugated bilirubin elevation).
- Grade 4 thrombocytopenia for ≥ 7 days, or Grade ≥ 3 thrombocytopenia associated with bleeding.
- Grade 4 neutropenia for ≥ 7 days, or Grade ≥ 3 neutropenia associated with infection.
- Febrile neutropenia of any grade.
- Any Grade ≥ 3 nonhematological toxicity (other than Grade 3 nausea, vomiting, or diarrhea ≤ 72 hours in duration with adequate prophylactic and supportive care).
- A severe hypersensitivity reaction (including anaphylaxis): the IMP must immediately be permanently discontinued and appropriate treatment instituted.

Study treatment must be discontinued if a female patient becomes pregnant.

6.4.8 Infusion supplies

The sponsor will supply syringes, vial adapters, infusion sets, ambulatory syringe infusion pumps, and any other supplies needed for the safe home IMP administration as required. Refer to the pharmacy manual for further details.

6.4.9 Blinding and unblinding

6.4.9.1 IMP blinding

Active and placebo product will be of identical appearance.

The IMP blind will be maintained through the Week 24 primary endpoint analysis. Patients, the sponsor, investigators, CROs and all study site personnel involved with the study, carrying out study procedures, evaluating patients, entering study data, and/or evaluating study data will remain blinded to treatment allocations until all patients have completed the Week 24 assessments and the database has been locked for the analysis at Week 24.

After Week 24, all patients will receive open-label pegcetacoplan.

6.4.9.2 IMP unblinding

6.4.9.2.1 Emergency unblinding

Unblinding, i.e., breaking the code for an individual patient during the study, is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment assignment is necessary for the proper handling of the patient. Emergency unblinding will be performed through IRT system.

The investigator should use best judgment, based on the nature and urgency of the clinical situation, and proceed with unblinding through IRT in situations in which knowledge of the patient's treatment assignment is necessary for clinical management. Once a patient's treatment assignment has been unblinded, the study medical monitor and study coordinator should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (e.g., date and time of the call to the medical monitor by the investigator, reason for unblinding, and date and time of unblinding) shall be clearly recorded in the patient's study file and in the EDC system as part of relevant standard operating procedures. In addition, the investigator should consider whether the clinical event prompting unblinding should be considered an AE or SAE according to the criteria for AEs or SAEs (see Section 6.5.4.1.1), and if so, such event shall be reported accordingly (see Section 6.5.4.1.2).

6.4.9.2.2 Unblinding for suspected unexpected serious adverse reactions

When a SUSAR occurs for a patient participating in the study, Sobi Global Pharmacovigilance & Patient Safety will request the unblinding of the treatment assignment. The randomization code will not be communicated to the site staff, or to the Sobi study team; unblinded SUSAR information will be provided to respective Health Authorities.

Please refer to the study manuals for further details of randomization and unblinding.

6.4.10 Prior and concomitant therapy

6.4.10.1 Permitted concomitant therapy

All medications administered and procedures performed within 12 weeks before ICF signature will be recorded as prior medications and procedures. Medications administered and procedures performed from the time of informed consent through the EOS visit are regarded as concomitant and will be documented as such.

Concomitant medications refer to all treatment taken between the dates of the first dose of IMP and the end of the follow-up period, inclusive. Concomitant medication information must be recorded on the appropriate eCRF page. With the exception of prohibited medications any concomitant medications deemed necessary for the patient's standard of care or wellbeing during the study or for the treatment of any AE may be given at the discretion of the investigator. It is the responsibility of the investigator to ensure that the details regarding all medications are recorded in full in the patient's eCRF.

The following concomitant medications are permitted only if administration is continued on a stable regimen (i.e., the dose has not changed for specific period defined below and is likely to remain unchanged during the study):

- Stable dosage for at least 4 weeks prior to randomization:
  - Bortezomib monotherapy.
  - Erythropoietin.
  - Corticosteroids. If a patient, per the investigator's opinion, requires corticosteroids initiation during the study for reasons other than CAD, a discussion with the study medical monitor is required before starting treatment. Topical, inhalation or intraarticular use of corticosteroids is permitted.
  - Vitamin K antagonists (e.g., warfarin) with a stable INR.
  - Direct oral anticoagulants.
  - Iron supplements, vitamin B_{12} or folic acid. If patients have previously received and tolerated iron chelation, this may be continued or reinitiated throughout the study if clinically indicated and upon discussion with the study medical monitor.
  - Low-molecular-weight heparin.
- Stable dosage for at least 8 weeks prior to randomization:
  - Immunosuppressants.
- Stable dosage for at least 14 weeks prior to randomization:
  - Belimumab monotherapy.

If clinically indicated and deemed in the best interest of the patient, the frequency or dose level of any of the above may be adjusted by the investigator in consultation with the study medical monitor.

COVID-19 vaccination is allowed during the study and should be administered according to the respective label.

6.4.10.2 Prohibited medications

Other than pegcetacoplan, any therapy for CAD is prohibited during patient's participation in the study, including:

- Rituximab (alone or in combination).
- Any other complement inhibitor (e.g., eculizumab, ravulizumab, or sutimlimab).
- Any other investigational drug.
- Plasma exchange.

Phlebotomy/venesection for iron overload is also prohibited.

6.4.11 Treatment compliance

Dosing diaries will be utilized for pegcetacoplan and are to be completed for each dose administered at the study site or outside regular clinic visits. Patients should not deviate from their dosing schedule.

When patients are dosed at the site, they will receive pegcetacoplan directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in eCRF. The dose of pegcetacoplan and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When patients self-administer pegcetacoplan at home, compliance will be assessed at each visit. Patients must be instructed to bring their empty/partially used/unused IMP packaging to every visit following randomization. Compliance will be assessed during the site visits and documented in the source documents and eCRF.

The pharmacist/designee will record details on the drug accountability form. Refer to the pharmacy manual for further details.

6.4.12 IMP accountability

Accountability and maintenance of the IMP at the study center is the responsibility of the investigator. The investigator will ensure that the IMP is used only in accordance with this study protocol. Where allowed, the investigator may choose to delegate drug accountability responsibilities to a pharmacist or other appropriate individual.

Investigators will be provided with the IMP to carry out this protocol for the agreed number of patients. The investigator/designee will acknowledge receipt of the IMP, and documenting shipment content and condition. Accurate records of all IMP dispensed, used/unused, returned, and/or destroyed must be maintained. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. The sponsor/designee will review IMP accountability at the study center on an ongoing basis during monitoring visits.

The IMP must not be used for any purpose other than the present study. IMP that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

The investigator is responsible for ensuring the retrieval of all returnable study supplies from patients.

6.4.13 IMP disposal

All unused and used IMP vials should be retained at the center until accountability and reconciliation has been performed by the study monitor. At the conclusion of the study, any unused IMP will either be destroyed at the investigator site or be returned to the sponsor/designee for destruction, and destruction will be documented appropriately. If no supplies remain, this fact will be documented appropriately.

6.5 Efficacy, safety, pharmacokinetic, pharmacodynamic and other assessments

6.5.1 Medical history

Medical history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the patient's preexisting conditions, including all prior significant illnesses, up to and including 1 year before screening. Information on CAD history will be collected including all prior lines of therapy. Additional preexisting conditions, present at the time when informed consent is given, up to the time of first dosing, are to be regarded as concomitant. The number of transfusions received during the 6-month period prior to randomization in this study will be recorded. Medical history will also include alcohol consumption and smoking history, if applicable.

Illnesses first occurring or detected during the study and worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 6.5.4.1.2.

6.5.2 Demography

Demographic data, including age, sex, race and ethnicity, will be collected for all patients, as allowed, per applicable regulations and recorded in the eCRF.

6.5.3 Efficacy assessments

6.5.3.1 Hb level and other laboratory efficacy assessments

The primary and other secondary efficacy assessments (i.e., Hb and LDH, haptoglobin, indirect bilirubin, ARC and D-dimer) are based on laboratory parameters and are described in Section 6.5.4.2.

For the primary efficacy assessment, response is defined as an increase in Hb level of ≥ 1.5 g/dL from Baseline or Hb normalization defined as change to within normal range (between the defined ULN and LLN) and maintenance of this effect from Week 16 to Week 24.

6.5.3.2 Transfusions

All the RBC transfusions performed during the study period from screening until end of the study will be recorded.

6.5.3.3 Health-related quality of life

The FACT-An is a useful measure of quality of life in cancer patients that adds focus to the widespread clinical problems of anemia [11]. It is a 5-point Likert-type scale and consists of 47 items: 27 items related to general quality of life (including physical, social, emotional and functional wellbeing) and 20 items related to the impact of fatigue (FACIT-F subscale) and other anemia-related symptoms (see Appendix 2 for informative purpose).

The SF-12 is a self-reported outcome measure assessing the impact of health on an individual's everyday life [12]. It is based on a subset of 12 items from the 36-Item Short Form Survey and assesses the same 8 health domains as its predecessor, with 1 or 2 questions per domain: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health (see Appendix 3 for informative purpose).

The EQ-5D-5L is a standardized instrument for measuring generic health status [13]. It consists of 2 pages: the descriptive system (comprising 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with 5 levels for each dimension) and a visual analog scale (to record the patient's self-rated health) (see Appendix 4 for informative purpose).

6.5.3.4 Appropriateness of efficacy measurements

The methods and measurements used for efficacy during the study (Hb and other laboratory parameters, number of transfusions and health-related quality of life tools) were used to determine responses to IMP and were appropriate measures to assess the efficacy objectives.

6.5.4 Safety assessments

6.5.4.1 Adverse events

6.5.4.1.1 Definitions

Adverse event

An AE is any untoward medical occurrence in a patient or study subject during the course of the study (after signing of the informed consent), whether or not considered by the investigator as related to study treatment.

AEs include the following:

- Abnormal test findings, as specified below.
- Changes in physical examination findings.
- Progression/worsening of underlying disease.
- Signs and symptoms resulting from overdose, withdrawal of treatment, drug-drug interactions, abuse and misuse.
- Increase in frequency or intensity of a preexisting episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study.

For pregnancies and breastfeeding, see Section 6.5.4.1.5.

Abnormal test findings

An abnormal test finding, e.g. abnormal laboratory analysis results, vital signs or ECG, should be recorded as an AE in any of the following situations:

- The investigator considers the abnormal test finding to be clinically significant.
- The abnormal test finding leads to a medical/surgical intervention including withdrawal of IMP(s) or discontinuation from the study. Repeat/confirmatory testing is not considered a medical intervention.

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.

AEs diagnosis versus signs/symptoms

For any AE, a diagnosis should be recorded rather than individual signs and symptoms or abnormal laboratory findings. However, if at the time of AE reporting a diagnosis is not available, each individual sign/symptom should be recorded. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be removed and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the start date of the first symptom of the eventual diagnosis. This approach also applies to signs and symptoms of CAD worsening, which should be reported as "CAD worsening/progression" or similar (e.g., relapse, flare progression or exacerbation), as appropriate.

Procedures

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy entered in the comments section of the eCRF.

Treatment-emergent adverse event

A treatment-emergent AE is any AE temporally associated with the use of study treatment, i.e., from study treatment initiation until 8 weeks after study treatment discontinuation.

Serious adverse event

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 subject or 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.

Serious also includes any other event that the investigator or company judges to be serious. Any suspected transmission of an infectious agent via IMP shall also be considered serious.

Hospitalization

In general, hospitalization means that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

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:

- Pre-planned hospitalization due to a preexisting condition not associated with a worsening of the preexisting condition.
- Protocol specified admission.
- Elective admission, e.g., due to cosmetic surgery.
- Social admittance (e.g., stay overnight due to travel reasons).

Complications that occur during hospitalization should not be considered SAEs unless the complication prolongs hospitalization.

Suspected unexpected serious adverse reaction

A SUSAR is an untoward and unintended response to a study drug that is not listed in the reference safety information of the IB, meets at least 1 of the seriousness criteria, and is assessed as causally related to the IMP.

6.5.4.1.2 Adverse event reporting period

The AE/SAE reporting period will be as follows:

Screening period: Any SAEs occurring between signing of the ICF and the first IMP dose should be reported to Sobi.

Treatment, maintenance and follow-up period: All AEs (including SAEs) occurring upon receiving the first IMP dose up to 8 weeks after last IMP administration must be recorded in the AE pages of the eCRF. In addition, SAEs should be reported to Sobi (see Section 6.5.4.1.4).

After follow-up period: New SAEs occurring at any time after the 8-week AE follow-up period should be reported to Sobi only if considered causally related to previous exposure to the IMP by the investigator. These SAEs are only entered in the drug safety database and, hence, will not affect study closure.

6.5.4.1.3 Obtaining and recording adverse event information

The investigator obtains AE information that is directly observed or solicited from the patient or patient relative during the course of the study. All AEs must be recorded in the eCRF using concise medical terminology.

The investigator is responsible for obtaining sufficient information to determine seriousness, causality and outcome of each AE.

Severity assessment

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum severity of the AE. For the purpose of consistency, these severity grades are defined as follows:

MILD	Does not interfere with patient's usual function
MODERATE	Interferes to some extent with patient's usual function
SEVERE	Interferes significantly with patient's usual function

Note the distinction between the gravity (seriousness) and the severity of an AE. **Severe** is a measure of intensity; thus, a **severe** event is not necessarily a **serious** event. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

Causality assessment

For each AE, the investigator must make a causality assessment to determine if there is a reasonable possibility that the IMP(s) caused the AE. The AE is assessed as **related** or **not related** to the IMP(s).

6.5.4.1.3.1 Reporting of adverse event to an auxiliary medicinal product

All AEs occurring after initiation of AxMP should also be reported in line with the reporting requirements stated above. Relationship to AxMp should be stated.

6.5.4.1.4 Serious adverse event reporting

Both serious and nonserious AEs are to be reported on the AE page of the eCRF as specified in the eCRF instructions.

In addition, all SAEs must be reported by the investigator to the Sobi Global Pharmacovigilance & Patient Safety within 24 hours of the investigator's first knowledge of the event.

If an SAE occurs, it is to be notified by e-mail (e-mail address is indicated on the SAE form) using the designated Serious Adverse Event form.

The SAE collection form is not always the same as the AE eCRF form. The forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

All new information obtained, relevant to an SAE report, should be forwarded to Sobi Global Pharmacovigilance & Patient Safety within the same timeframe as the initial information.

If the patient is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE-relevant information and documentation.

New SAEs occurring after the 8-week AE follow-up period must be reported to Sobi Global Pharmacovigilance & Patient Safety within 24 hours of the investigator's knowledge of the event, only if considered causally related to previous exposure to the study treatment by the investigator.

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

The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to Health Authorities, IRBs/IECs, and investigators is the reference safety information section of the IB.

6.5.4.1.4.1 Reporting of serious adverse event to an auxiliary medicinal product

All SAEs occurring after initiation of AxMP should also be reported in line with the reporting requirements stated above. Relationship to AxMp should be stated.

6.5.4.1.5 Exposure during pregnancy and breastfeeding

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Any pregnancy occurring after study initiation (i.e., signing of ICF) up to 90 days following study treatment discontinuation must be reported within 24 hours of the investigator's knowledge of the event. This includes all situations where a woman is or has been found to be pregnant after being exposed to IMP – directly, indirectly or via her partner (paternal exposure).

All events of exposure to the IMP during pregnancy (female patient or male patient's partner) or breastfeeding, whether the exposure is associated with an AE or not, shall be reported to Sobi Global Pharmacovigilance & Patient Safety by e-mail using pregnancy notification form by e-mail (e-mail address is indicated on the pregnancy notification form).

In all reported situations of exposure during pregnancy, Sobi will provide the investigator with a Pregnancy report form that shall be completed and returned by the investigator. The investigator is responsible for monitoring the outcome of the pregnancy and to inform Sobi Global Pharmacovigilance & Patient Safety of relevant information and any information requested related to the outcome of the pregnancy.

Any AEs and SAEs observed during and in relation to pregnancy, delivery or breastfeeding should be recorded in the eCRF and, as applicable, be reported to Sobi Global Pharmacovigilance & Patient Safety as described previously in this section.

6.5.4.1.6 Follow-up of unresolved adverse events

All 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 last scheduled visit. How to report changes in an ongoing AE during a patient's participation in the study is described in the eCRF instructions.

In addition, all serious and nonserious AEs assessed by the investigator as related to the IMP 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.

6.5.4.2 Laboratory assessments

Laboratory assessment samples (Table 4) are to be obtained at designated visits as detailed in the schedule of assessments (Table 1 and Table 2).

Table 4 Laboratory assessments

Hematology	Hb ARC Hematocrit MCH, MCHC and MCV	Platelet count RBC count WBC count with differential
Serum chemistry	Albumin ALT ALP AST Bilirubin (total, direct, and indirect) BUN Calcium Chloride Creatinine Creatine kinase	Estimated glomerular filtration rate (using CKD-EPI formula) GGT Glucose Haptoglobin LDH Phosphorus Potassium Sodium Uric acid
Urine studies	Urinalysis Bile Blood Glucose Ketones Leukocyte esterase	Nitrite Pregnancy, when applicable Protein Specific gravity Urobilinogen Albumin-to-creatinine ratio
Coagulation [a]	aPTT D-dimer Fibrinogen	INR Thrombin-antithrombin complex
Additional	Serum pregnancy test FSH (postmenopausal women) HBV-DNA HCV-RNA HIV *Mycoplasma pneumoniae* EBV DNA Folate Vitamin B12 Ferritin Iron TNFα, IL-6, IL-10, IFNγ and IL-1β	Complement activation tests: C3, functional assays for classical and alternative complement pathways Anti-pegcetacoplan peptide/anti-PEG Ab Immunoglobulins quantitative (IgG, IgM and IgA) DAT monospecific C3 and IgG Flow cytometry for C3 deposition on RBCs Serum cold agglutinin titer (at 4 °C) Antinuclear antibodies

Abbreviations: Ab, Antibody; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; aPTT, Activated partial thromboplastin time; ARC, Absolute reticulocyte counts; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; C3, Complement component 3; CKD-EPI, Chronic Kidney Disease – Epidemiology Collaboration; DAT, Direct antiglobulin test; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; FSH, Follicle-stimulating hormone; GGT, Gamma-glutamyltransferase; Hb, Hemoglobin; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; IFNγ, Interferon-gamma; Ig, Immunoglobulin; IL, Interleukin;

INR, International normalized ratio; LDH, Lactate dehydrogenase; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; MCV, Mean corpuscular volume; PEG, Polyethylene glycol; RBC, Red blood cells; RNA, ribonucleic acid; TNFα, Tumor necrosis factor-alpha; WBC, White blood cells.
[a] The use of silica reagents in coagulation panels should be avoided in all patients.

Blood and urine samples will be analyzed at a central laboratory unless a local laboratory facility is necessary, as defined in the laboratory manual. Urine samples will be analyzed by dipstick and microscopic analysis. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the patient's eCRF and medical record (source document) for that visit.

Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (see Section 6.5.4.1.1 for details). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

The use of silica reagents in coagulation panels should be avoided. The sponsor previously conducted an investigation into prolonged aPTTs observed in subjects treated with pegcetacoplan. It was confirmed that false-positive aPTT prolongation occurred when coagulation panels were performed using a Stago Analyzer and, specifically, silica reagents. It was determined that there was interference between the silica reagents and PEGylated pegcetacoplan, resulting in artificially prolonged aPTTs.

If a patient has been tested for COVID-19, the results, if available, will be documented in the eCRF.

6.5.4.2.1 Pregnancy tests

For WOCBP, a serum pregnancy test will be performed at screening. A urine pregnancy test will also be performed every 4 weeks through the end of the study, including the Follow-up visit, by using a home test if there is no clinic visit. Patients with positive results will be excluded or discontinued from the study. Urine pregnancy test will be completed prior to dosing on days where dosing coincides with clinic visits.

6.5.4.3 Anti-pegcetacoplan peptide antibody and anti-PEG antibody assessments

Patients will have anti-pegcetacoplan peptide Ab and anti-PEG Ab samples collected as outlined in the schedule of assessments (Table 1 and Table 2). The proposed ADA sampling schedule was established to capture the ADA signal at Baseline, any potential early onset and the dynamic profile (transient or persistent) of Ab formation while minimizing pegcetacoplan level in the sample.

Patients who are confirmed as having positive results for anti-pegcetacoplan peptide or anti-PEG Ab in the last dosed sample will be followed up with ADA samples being collected every 6 months until the Ab levels return to baseline. Specific Ab titers will be determined in all samples that are confirmed positive for anti-pegcetacoplan peptide or anti-PEG Ab. Any samples

that are confirmed positive for anti-pegcetacoplan peptide Ab will be further characterized with a neutralizing Ab assay.

6.5.4.4 Vital signs

Vital signs (body temperature, respiration rate, heart rate and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the schedule of assessments (Table 1 and Table 2). All vital signs will be measured after the patient has been resting in a sitting position for at least 5 minutes, except when supine or semi-reclined because of study procedures and/or AEs or if deemed necessary by the investigator. Blood pressure measurements are to be taken in the same arm for the duration of the study.

When the IMP is administered at the study site, vital signs will be measured within 2 hours before dosing and venipuncture (and ECG, if applicable) and at 30 minutes (± 5 minutes) post dose.

Vital signs measurements will be repeated, if clinically significant or if machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements will be repeated at the investigator's discretion. Any confirmed, clinically significant vital signs measurements must be reported as AEs (see Section 6.5.4.1.1 for details).

6.5.4.5 Weight and height

Body weight and height (both assessed without shoes on) will be recorded at screening. Weight will also be recorded at each physical examination.

6.5.4.6 Physical examination

Full physical examinations performed by the investigator/designee will include assessment of the following items: general; head, ears, eyes, nose, and throat; dentition; thyroid (endocrine); heart; chest; lungs; abdomen; skin; extremities; back/neck; musculoskeletal system and lymph nodes.

Brief physical examinations will include general appearance, heart, lungs, abdomen and extremities, and are to be performed at all visits where a full physical examination does not occur.

See the schedule of assessments (Table 1 and Table 2) for the details regarding which type of physical examination should be performed at each visit.

If any abnormalities are reported at screening, they should be recorded as medical history. New or worsening of abnormalities after first IMP dosing should be reported as AEs (see Section 6.5.4.1.1 for details).

6.5.4.7 Electrocardiograms

Single 12-lead ECGs will be measured prior to dosing at the time points outlined in the schedule of assessments (Table 1 and Table 2). The ECG will be taken after the patient has been resting in

the supine position for 5 minutes in a quiet environment and prior to any blood sampling procedures, unless specified at time points after timed blood sampling procedures.

The ECGs will be classified as normal, having a not clinically significant abnormality or having a clinically significant abnormality.

Any significant ECG finding present prior to the start of study drug is to be documented in the medical history section of the eCRF. Any significant ECG finding with an onset time after study drug initiation and that were not present at screening, or worsened during the study, is to be reported as AEs (see Section 6.5.4.1.1 for details).

6.5.4.8 Infusion-site reactions/pump-safety assessments

If the scheduled dosing day coincides with a clinical visit, the patient or their caregiver should perform their infusion at the clinic in presence of the investigator or other trained and qualified site staff. Patients or their caregivers will be trained to administer at home.

On the days of clinic visits, an assessment of the pegcetacoplan infusion site will be made as a part of the AE assessment. If pegcetacoplan is administered at the visit, the site staff will observe the dosing, and pump use safety will be assessed. The infusion site will be checked again within 30 minutes after study drug administration. The infusion-site assessments will be performed by an appropriately trained staff, as delegated by the investigator. The infusion site and surrounding area will be inspected for redness, swelling, induration and bruising. The patient will be asked about the presence of pain and/or tenderness, and any issue related to pump use. The date, time and outcome of the infusion-site assessment will be recorded on the source documents and eCRFs.

Patients will be instructed to notify the investigator or other study personnel in the event that an infusion-site reaction occurs after self-administration of pegcetacoplan. All clinically relevant AEs, as determined by the investigator, from infusion site or related to pump use will be recorded as AEs (see Section 6.5.4.1.1 for details).

6.5.4.9 Appropriateness of safety measurements

The methods and measurements used for safety during the study are standard and were appropriate for the clinical evaluation of the patients with CAD treated with pegcetacoplan.

6.5.5 Pharmacokinetic assessments

Blood sampling and processing blood samples for the PK assessment of pegcetacoplan will be collected via direct venipuncture at the time points outlined in the schedule of assessments (Table 1 and Table 2). PK samples will be taken 15 minutes predose at each visit.

Instructions for collection, handling, processing, storage, and shipping of samples will be provided in a separate sample handling manual prior to study initiation.

Serum sample analysis will be performed using validated LC-MS/MS methods. The methods used and the results obtained will be included in the CSR as an appendix.

Population PK and exposure-response modeling of the safety and efficacy data will be described in a pegcetacoplan Population PK/PD Analysis Plan and reported in a separate population PK report.

6.5.6 Pharmacodynamic assessments

Blood samples for PD assessment of hemolytic complement activation through functional assays for classical and alternative complement pathways will be collected on study days designated in the schedule of assessments (Table 1 and Table 2). Blood samples to measure C3 levels and C3 deposition on RBCs will also be collected. Instructions for collection, handling, processing, storage, and shipping of samples will be provided in a separate laboratory sample handling manual prior to study initiation.

The PD measurements in this study are widely used, generally recognized and accepted as reliable, accurate, relevant and consistent with those used in several other studies of pegcetacoplan.

6.5.7 Other study assessments

6.5.7.1 MYD88 mutation testing

Bone marrow biopsy will be performed at screening only if a biopsy was not previously undertaken within 1 year prior to ICF signature.

In those patients requiring a bone marrow biopsy for study purposes, genetic mutation testing of the MYD88 gene will be performed locally on aspirate during screening. If the MYD88 genetic mutation testing has been already performed according to the local institutional standard of care, the result will be collected at screening.

7 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study specific procedures, Sobi SOPs, CRO SOPs, the ICH Guideline for GCP [1], and applicable regulatory requirements.

The sponsor will systematically review the study quality management to identify, evaluate and control risks to study critical processes and data that 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.

Monitoring visits to the study site will be performed periodically during the study, to help ensure compliance with the protocol, study specific procedures and applicable regulatory requirements.

In case of new waves of restricted access to study sites due to the unforeseeable evolution of the COVID-19 pandemic, to ensure ongoing patients' rights, safety and wellbeing, and control risks to study critical processes, the sponsor might decide to apply alternative mechanisms of oversight and monitoring. Among these mechanisms, remote source data verification would be implemented only if allowed by country regulations and within the limits established.

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.

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

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

8 Statistical plan

A formal SAP will be developed and finalized prior to locking the database and unblinding of the study data. The full details of data presentations and analyses will be provided in the SAP. Additional statistical analyses other than those described in this section may be performed, if deemed appropriate, and included in the SAP. Any deviations from the final SAP or from what is outlined in the protocol will be discussed in the CSR.

8.1 Determination of sample size

The primary endpoint is response at Week 24. Under the assumption that the response rate is 55 % for pegcetacoplan and 10 % in placebo, 54 patients (36 treated with pegcetacoplan and 18 with placebo) are required to reject the null hypothesis of no difference between the treatment groups at a significance level of 5 % and a power of 90 % using a 2-sided Fisher's exact test with a 2:1 allocation to treatment groups. To account for potential drop out prior to first dose of IMP, 57 patients will be enrolled in the study.

8.2 Definition of study populations

8.2.1 Screened set

The screened set will include all patients who provide written informed consent. This set will be used only for the purpose of describing patient disposition.

8.2.2 Safety set

The safety set will include all patients who receive at least 1 dose of IMP. Patients will be analyzed according to the treatment they received.

8.2.3 Intent-to-treat set

The ITT set will include all randomized patients. Patients will be analyzed according to their assigned treatment, regardless of the treatment actually received.

8.2.4 Modified intent-to-treat set

The mITT set will include all patients in the ITT set who continue IMP beyond Week 4.

8.2.5 Per-protocol set

The PP set will include all patients in the ITT set who have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. Decisions concerning the exclusion of patients from the PP analysis set will be made and documented prior to database lock.

8.2.6 Pharmacokinetic set

The PK set will include all patients in the ITT set who receive IMP and have at least 1 evaluable post dose PK measurement.

8.2.7 Pharmacodynamic set

The PD set will include all patients in the ITT set who receive IMP and have at least 1 evaluable post dose PD measurement.

8.3 Overall statistical and analytical plan

All details of the statistical analyses for primary and secondary endpoints will be described in the SAP, which will be finalized and signed off prior to breaking the blind after Part A.

8.3.1 General statistical issues

All statistical tests will be 2-sided and performed at a significance level of 5 % unless otherwise stated.

8.3.2 Demographics and baseline characteristics

Demographics, baseline characteristics, concomitant medications/treatments, medical history, and IMP exposure will be summarized by treatment group.

The WHO and MedDRA coding dictionaries will be used for the concomitant medications/treatments and medical histories, respectively.

8.3.3 Analysis related to primary objective

The primary efficacy endpoint is a responder analysis, where response is defined as an increase in Hb level of ≥ 1.5 g/dL from Baseline or Hb normalization and maintenance of this effect from Week 16 to Week 24, in the absence of PRBC transfusions (between Week 5 and Week 24). Hb normalization is defined as within normal range (between the defined ULN and LLN), as set by the testing laboratory. The primary efficacy analysis will be conducted on the ITT set. Maintenance of effect is defined as the average change from Baseline in Hb of Week 16, Week 20 and Week 24 ≥ 1.5 g/dL or the average Hb at these time points within normal range.

The estimand will be a composite where patients having an ICE will be considered as nonresponders. The ICEs of interest are:

- Withdrawal from treatment or lost to follow-up before end of the double-blind period.
- Use of prohibited medications (rituximab alone or in combination, any other complement inhibitor, any other investigational drug and plasma exchange).

The number and percentage of patients who respond will be tabulated by treatment group and compared between treatment groups using a Fisher's exact test. The odds ratio of being a responder for the pegcetacoplan treatment group versus the placebo group and associated exact 95 % CI will be provided. In case of 0 events, the difference in responder rate will also be reported.

The following will be included as supportive analyses:

- Analyses will be repeated using the PP set and mITT set.

Other sensitivity analyses will be explored, and details will be provided in the SAP.

Subgroup analyses on the primary endpoint will be conducted for:

- The strata with ≥ 1 / 0 transfusions during the 6 months prior to randomization.
- The subgroups of patients previously treated with rituximab / rituximab-naïve patients.

Other potential subgroups of interest will be described in the SAP.

Baseline will be taken at Day 1 prior to the start of IMP treatment.

8.3.4 Analysis related to secondary objectives

8.3.4.1 Analysis of key secondary efficacy endpoints

The key secondary efficacy endpoints are described in Section 5.2.1.1.

The change from Baseline to Week 24 in Hb will be analyzed using MMRM with the fixed effects of treatment, strata, visit, visit-by-treatment interaction and Hb level at Baseline as covariate using an unstructured covariance matrix and the Kenward-Roger method for calculating the degrees of freedom. Should the model fail to converge with an unstructured covariance matrix other covariance structures will be explored. Details will be described in the SAP. The difference between treatment groups will be estimated, along with its 95 % CI and p-value.

The ICEs for the change from Baseline to Week 24 in Hb analysis are the following:

- Withdrawal from treatment or lost to follow-up before end of the double-blind period (all legitimately recorded values will be used).
- Use of prohibited medications (all measurements after prohibited medication start date will be set to missing).
- Transfusion from Week 5 to Week 24 (all measurements after transfusion will be set to missing).

The endpoint will be analyzed using MMRM which will implicitly impute data after ICE and result in a hypothetical strategy to handle the ICEs.

Transfusion avoidance (Yes/No) from Week 5 to Week 24 (total population) will be tabulated by treatment group and compared between treatment groups using Fisher's exact test. The odds ratio of showing transfusion avoidance from Week 5 to Week 24 for the pegcetacoplan treatment group versus the placebo group and associated 95 % CI will be provided. The composite strategy is used as estimand where patients meeting any of the intercurrent events defined for primary endpoint will be considered as failures.

The change from Baseline at Week 24 in the FACT-An score will be analyzed using MMRM with the fixed effects of treatment, strata, visit, visit-by-treatment interaction and the FACT-An score at Baseline as covariate using an unstructured covariance matrix and the Kenward rogers method for calculating the degrees of freedom. Should the model fail to converge with an

unstructured covariance matrix other covariance structures will be explored. Details will be described in the SAP. The difference between treatment groups will be estimated, along with its 95 % CI and p-value. The ICEs and the strategy for handling them for the analysis of change from Baseline at Week 24 in the FACT-An score will be the same as that for the analysis of change from Baseline to Week 24 in Hb, as described above.

To preserve the Type 1 error, a fixed-sequence testing strategy will be used; hence, statistical significance with the first key secondary endpoint will only be concluded if statistical significance is achieved with the primary analysis of the primary endpoint. The ordering of the key secondary endpoints in this testing strategy will match the order in which they are presented in Section 5.2.1.1, i.e., change from Baseline to Week 24 in Hb level, transfusion avoidance (Yes/No) from Week 5 to Week 24 and change from Baseline to Week 24 in the FACT-An score. The hierarchical testing will be applied to the primary and key secondary endpoints, no further multiplicity control will be applied.

For all key secondary endpoints, subgroup analyses will be conducted for the strata (≥ 1 / 0 transfusions during the 6 months prior to randomization) and for the subgroups of patients previously treated with rituximab / rituximab-naïve patients. Other potential subgroups of interest will be described in the SAP.

8.3.4.2 Analysis of secondary efficacy endpoints: Part A

Baseline measurements will be taken at Day 1, prior to the start of IMP treatment.

All secondary efficacy analyses will be analyzed with the ITT set.

The number of PRBC transfusions from Week 5 to Week 24 in each treatment group will be compared using a negative binomial regression model. The model-based estimate of the treatment effect and corresponding 95 % CI will be calculated.

The change from Baseline at Week 24 in LDH, haptoglobin, indirect bilirubin, ARC and D-dimer will be analyzed using MMRM analysis with the fixed effects of treatment, strata, visit, visit-by-treatment interaction, and the respective Baseline level as covariate, using an unstructured covariance matrix and the Kenward-Roger method for calculating the degrees of freedom. Should the model fail to converge with an unstructured covariance matrix, other covariance structures will be explored. Details will be described in the SAP. The difference between treatment groups will be estimated, along with its 95 % CI and p-value.

For the endpoint regarding the normalization of markers of hemolysis (LDH, indirect bilirubin and ARC), at Week 24, the number and percentage of patients who respond will be tabulated by treatment group and compared between treatment groups using a Fisher's exact test.

Kaplan-Meier plots will be presented for the time-to-event endpoints of time to normalization from Baseline to Week 24 for LDH, Hb, indirect bilirubin and ARC for each treatment group at Week 24, and survival estimates will be provided.

The number of units of PRBCs transfused from Week 5 to Week 24 in each treatment group will be compared using a Wilcoxon rank-sum test. The difference between the medians will be estimated along with its 95 % CI. Patients who withdraw before Week 24 will have the number of units estimated from the duration that they were in the study.

The change from Baseline at Week 24 in FACIT-F, SF-12 and EQ-5D-5L will be analyzed using MMRM with the fixed effects of treatment, strata, visit, visit-by-treatment interaction and the respective Baseline level as covariate, using an unstructured covariance matrix and the Kenward-Roger method for calculating the degrees of freedom. Should the model fail to converge with an unstructured covariance matrix other covariance structures will be explored. Details will be described in the SAP. The difference between treatment groups will be estimated, along with its 95 % CI and p-value.

Summary statistics by treatment groups will be presented at each assessment visit during the 24-week double-blind treatment period.

8.3.4.3 Analysis of secondary efficacy endpoints: Part B

Baseline measurements will be taken at Day 1, prior to the start of IMP treatment.

All Part B secondary efficacy analyses will be analyzed with the ITT set, and data presentations will be by randomized treatment group in Part A as well as combined.

The change from Baseline at Week 48 in Hb, LDH, indirect bilirubin, ARC and D-dimer will be analyzed using descriptive statistics.

Durability of response is the time until response is lost; response is lost at the first time point when the average change from baseline in Hb is < 1.5 g/dL (the average of all time points from Week 16) or the patient receives a transfusion or the patient discontinues treatment or the study. Durability of response will be analyzed as a time to event variable with Kaplan-Meier statistics provided. Only patients randomized to pegcetacoplan in Part A who achieved the primary endpoint at Week 24 will be included in this analysis. The time to event will be defined as the time the patient achieved the primary endpoint at Week 24 until the earliest time durability of response (as defined above) is lost.

For the endpoint regarding the normalization of markers of hemolysis (LDH, indirect bilirubin and ARC), at Week 48, the number and percentage of patients who respond will be tabulated in frequency tables by randomized treatment group in Part A as well as combined.

The change from Baseline at Week 48 in FACT-An, SF-12 and EQ-5D-5L will be analyzed using descriptive statistics.

8.3.4.4 Analysis of tertiary efficacy endpoints: Part C

Baseline measurements will be taken at Day 1, prior to the start of IMP treatment.

All tertiary efficacy analyses will be analyzed with the ITT set and data presentations will be by randomized treatment group in Part A as well as combined.

The change from Baseline at Week 96 in Hb, LDH, haptoglobin, indirect bilirubin, ARC and D-dimer will be analyzed using descriptive statistics.

For the endpoint regarding the normalization of markers of hemolysis (LDH, indirect bilirubin and ARC), at Week 96, the number and percentage of patients who respond will be tabulated in frequency tables by randomized treatment group in Part A as well as combined.

The change from Baseline at Week 96 in FACT-An, SF-12 and EQ-5D-5L will be analyzed using descriptive statistics.

8.3.4.5 Analysis of exploratory endpoints.

All exploratory endpoints will be summarized descriptively. Further details will be described in the SAP.

8.3.5 Analysis of safety and tolerability data

All safety analyses will be carried out descriptively on the safety set, consisting of all patients who received at least 1 dose of IMP.

In general, the evaluation of safety and tolerability is carried out separately for the double-blind placebo-controlled period and the open-label period. Other analyses are detailed in the SAP.

Pretreatment AEs are those occurring between ICF signature and the first IMP administration. TEAEs are defined as those AEs that develop or worsen after the first dose of IMP and up to 8 weeks after the last dose of study medication.

All AEs will be coded using the MedDRA. Pretreatment AEs will be summarized by SOC and PT. TEAEs will be summarized by SOC, PT, treatment group for number of patients and proportion reporting the event. A similar summary will be produced for SAEs, AEs leading to premature discontinuation of IMP and AEs related to the IMP. The intensity of AEs and the relationship to the IMP will be summarized for each SOC and PT by treatment group.

AEs leading to IMP discontinuation will be summarized by frequency tables.

The results of laboratory assessments, anti-pegcetacoplan peptide/anti-PEG Ab assessments, vital signs and ECGs will be summarized by treatment group using appropriate descriptive statistics.

The AE summaries will be presented across all patients. All AEs will be listed by patient, along with information regarding onset, duration, relationship to IMP, severity, action taken with IMP, treatment of event and outcome.

Changes from Baseline in clinical laboratory test results will be summarized using descriptive statistics. Baseline will be taken as the measurement closest, but prior, to randomization. Out-of-range values will be flagged in data listings.

Laboratory data and vital signs will be graded for severity using CTCAE v 5.0 and all grade ≥ 3 results will be considered clinically meaningful.

Changes in physical examinations will be described in a data listing.

Safety data will include all data up to Week 24 for reporting Part A, all data up to Week 48 for reporting Part B, and all data for reporting Part C.

8.3.6 Analysis of pharmacokinetic and pharmacodynamic

8.3.6.1 Pharmacokinetic analysis

The PK concentrations will be evaluated using the PK set.

Concentrations will be summarized, using descriptive statistics, over time, in the randomized treatment groups.

Individual patient concentration-time data will be plotted against actual sampling time. Median profiles of the concentration-time data, using nominal sampling times, will also be presented. Both linear-linear and linear-log plots will be presented.

Population PK and exposure-response modeling of the safety and efficacy data will be described in a pegcetacoplan Population PK/PD Analysis Plan.

8.3.6.2 Pharmacodynamic analysis

The PD endpoints will be evaluated using the PD set.

Absolute values, changes from Baseline and percentage changes from Baseline will be summarized using descriptive statistics, over time by treatment group.

Individual patient time profiles will be plotted against actual sampling time. Median profiles, over time, using nominal sampling time, will also be presented.

The PD endpoints in each treatment group will be compared using mixed effect repeated measures analyses.

8.3.7 Interim analysis

No formal interim analyses are planned for the primary endpoint. Data will be reported for Part A (double-blind treatment period) once all patients have completed their Week 24 visits (or have early discontinued) and the database has been cleaned and verified for all visits up to and including Week 24. Similarly, data will be reported after Part B.

8.3.8 Multiple comparison/multiplicity

Adjustments for multiple testing will be done among key secondary endpoints as described in Section 8.3.4.1.

8.3.9 Handling of missing data

Imputation of missing data (e.g., partial or missing dates) will be described in the SAP.

9 Data collection, handling and record keeping

9.1 Data standards

Collection of data should be performed in the CDASH format, according to the 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 format.

9.2 Case report form

An eCRF is required and should be completed for each included patient. In this study, a web based, password protected, EDC software tool will be used to collect, clean and process the study data. The EDC system will be provided and managed by the independent CRO. The designated investigator site staff will only be given access to the EDC system upon completion of the user training.

The data should be entered by site users into the EDC system on an ongoing basis. In principle, it is recommended to perform data entry within 5 working days from the visit date. To ensure data quality within EDC, an automated edit check will be triggered to verify the completeness and accuracy of input data.

It is the responsibility of the investigator to ensure completion and to review and approve all eCRFs. eCRFs must be signed electronically 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 clinical and laboratory data entered on the eCRFs.

The completed original eCRFs are the sole property of Sobi and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from Sobi.

9.3 Source data

Patient source documents are the patient's medical 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. In some cases, a portion of the source documents for a given patient may be the eCRF.

A separate source document location agreement will be completed and signed by the principal investigator and the site monitor before study start.

Source data should be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available (ALCOA+). 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).

9.4 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 to, 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 that the study medical monitor is notified. The study medical monitor 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 subject protection or the reliability of study results.

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

9.5 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 breaking of the blind and before generation of any results. The database lock will be approved by relevant study personnel,

and all edit accesses will be removed. The study database can only be unlocked in cases where critical errors, affecting the main conclusions of the study, are discovered.

9.6 Record retention

The investigator should maintain a record of the location(s) of investigator's essential documents as defined in the ICH GCP Guideline [1] 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 Health Authorities, 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 [1].

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.

10 End of study

The end of study is when all randomized patients have terminated the 8-week safety follow-up period and performed the EOS visit or the Early termination visit in case of discontinuation for any reason from the study before completion.

11 Sponsor's discontinuation criteria

Specific study stopping criteria are described in Section 6.3.6. 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 or administrative reasons. After such a decision, the investigator must contact all participating patients within 30 days and explain what treatment(s)/medical care is necessary and available according to local regulations, and patients will be treated according to local medical practice. All study materials must be collected, and all the eCRFs must be completed to the greatest extent possible.

12 Dissemination and publication of results

A CSR will be prepared for the primary analysis once all patients have completed their Week 24 visits and the database has been cleaned for all visits up to and including Week 24 (Part A). CSR addenda will be prepared to include open-label (Part B), maintenance (Part C) and follow-up data.

Sobi will register the study by posting study information and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations, e.g., on www.clinicaltrials.gov and EudraCT. The results of this study will be published within 12 months of the EOS.

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 [14].

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 shall not to be unreasonably withheld.

13 Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the sponsor. However, authorized regulatory officials, IRB/IEC personnel, the sponsor and its authorized representatives are allowed full access to the records.

All study patients must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient, who will be required to give consent for their data to be used as described in the ICF. The patients must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Identification of patients and eCRFs shall be by unique subject identification numbers only. All personal identifiers according to applicable regulations (eg, name, phone number) must be redacted permanently by the site personnel and replaced with the subject’s unique identification number in all records and data before transfer to the sponsor (or designee).

All personal details will be treated as confidential by the investigator and sponsor's or designated staff.

14 Reference list

1 ICH Harmonised Guideline: Integrated addendum to ICH E6 (R1), Guideline for Good Clinical Practice E6(R2) Current *Step 4* version dated 9 November 2016. Available from: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

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11 Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. Seminars in Hematology. 1997, 34(3, Suppl 2):13-19.

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Appendix 1 Additional protocol signatures

Sponsor's Clinical Program Leader

[redacted]
Clinical Program Leader
E-mail [redacted]

Signature

Date

Sponsor's Statistician

[redacted]
Statistical Science Director
E-mail [redacted]

Signature

Date

Appendix 2 Functional Assessment of Cancer Therapy–Anemia/Fatigue

FACT-An (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-An (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-An (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
An11	I have pain in my chest	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
An13	I am motivated to do my usual activities	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 3 12-Item Short Form Survey

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 4 EuroQol-5 Dimension-5 Level

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

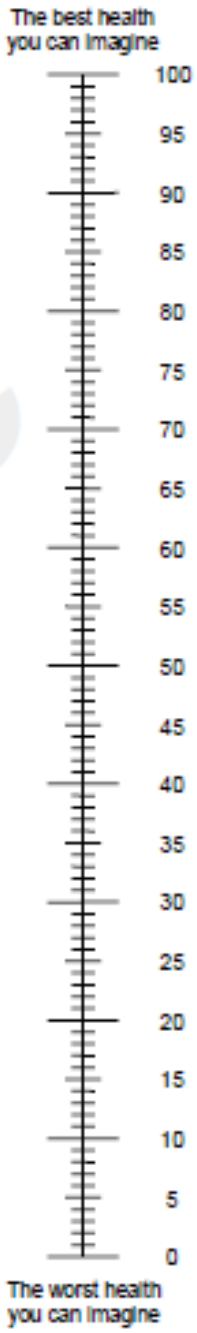
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

Appendix 5 Protocol changes to be followed during COVID-19 restrictions

OVERVIEW

In response to the COVID-19 crisis, to ensure the safety of study patients and investigative sites as well as proper conduct of the study, TEMPORARY changes to the protocol have been implemented. These changes should be followed only during COVID-19 restrictions and include extended IMP administration windows, rescreening instructions, and a revised schedule of assessments. These changes will be reported as COVID-19-related protocol deviations.

Where feasible, sites could continue to follow the full schedule of assessments.

In case of new waves of restricted access to study sites due to the unforeseeable evolution of the COVID-19 pandemic, to ensure ongoing patients' rights, safety and wellbeing, and control risks to study critical processes, the sponsor might decide to apply alternative mechanisms of oversight and monitoring. Among these mechanisms, remote source data verification would be implemented only if allowed by country regulations and within the limits established.

MINIMUM SCHEDULE OF ACTIVITIES

Where feasible, sites could continue to follow the full schedule of activities (based on their treatment group assignment). The minimum assessment tables, only to be followed during this COVID-19 effort and if determined necessary to use on the basis of the investigator's clinical judgment, are provided below to reduce the time required for each study visit. Assessments not performed (even those that have been removed in the minimum assessment table) should be documented.

Patients who are not able to come into the clinic for a study visit because of COVID-19-related restrictions, should be contacted via the phone for the collection of AEs (including SAEs) and concomitant medications. **All SAEs are still required to be reported within 24 hours of site awareness, even if reported via phone call**. All communications via phone call should also be documented in the source documentation and in the respective eCRF page. In addition, these patients should be instructed to self-monitor their symptoms at home and report any changes in symptoms or their overall health via phone call. The site must inform the sponsor of any patients lost to follow-up.

It is critical that local, country, and regional governance regarding COVID-19 is followed along with your best clinical judgment when managing this situation. All visits or assessments missed as a result of COVID-19 will be captured in the case report forms.

MINIMUM STUDY REQUIREMENTS

The following are the minimum study requirements for Study Sobi.PEGCET-101 during the COVID-19 pandemic and should be used as guidance when the full protocol requirements cannot be conducted.

1. **Obtain** key safety laboratory assessments.
    a. All laboratory assessments should be drawn at the frequency required by the minimized schedule of events (Table 5 and Table 6).
        i. Includes (at minimum): hematology with differential, reticulocyte count, chemistry including LDH, haptoglobin and bilirubin total, coagulation profile, and urine pregnancy test (only for women of childbearing potential).
    b. In the event that the clinical investigative site is closed or patients are unable/unwilling to travel, patients should be referred to a certified local laboratory that can perform the required safety testing (see schedule of events below). The investigator should collect the local laboratory reports, which must be redacted (e.g., name and other local requirements) and added to the study records.
2. **Perform** minimal medical safety assessments.
    a. If the patient is unable to have an in-person assessment, the investigator (or delegated site staff) should have a telephone contact at a frequency noted in the protocol (at minimum) to solicit AEs (including SAEs), concomitant medications and transfusions. The appropriate forms in the eCRF should be completed.
3. **Document** appropriate contact with the patient.
    a. Earnest and reasonable attempts must be made to solicit AEs and concomitant medications. The CRA/medical monitor must be notified of any patients lost to follow-up.
    b. All communication with the patient (including failed attempts at contact) must be documented in the study records.

The modified schedule of activities is shown in Table 5 and Table 6.

Table 5 Revised COVID-19 minimum schedule of assessments: Screening to Week 24 – Part A

Study Period	**Screening [a]**		**Part A: Double-blind treatment period**								
Study Week	**-4 to -1**	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24º**
Study Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**
Study Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit window (± days)	**0**		**0**	**1**	**2**	**7**	**7**	**7**	**7**	**7**	**7**
Informed consent	X										
Demographics	X										
Medical history	X										
RBC transfusions collection	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion criteria	X	X	X								
Randomization			X								
Vaccination [b]	X				X			X			
Prophylactic antibiotic administration [c]	According to local standard practices in patients who cannot be vaccinated										
Full physical examination [d]	X		X								X
Brief physical examination [e]				X	X	X	X	X	X	X	
Weight and height [f]	X		X	X	X	X	X	X	X	X	X
12-lead ECG (prior to venipuncture)	X		X								X
IMP administration [g]			Twice weekly----------→								
Infusion-site assessment [h]			X	X	X	X	X	X	X	X	X
Concomitant medications/treatments	X		X	X	X	X	X	X	X	X	X
Vital sign measurements [i]	X		X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X
Urine studies	X	X				X	X	X	X	X	X
Blood [k]		X		X	X	X	X	X	X	X	X
Pharmacokinetics [m]		X		~~X~~	~~X~~	~~X~~		~~X~~			X

Table 5 Revised COVID-19 minimum schedule of assessments: Screening to Week 24 – Part A

Study Period	**Screening [a]**		**Part A: Double-blind treatment period**								
Study Week	**-4 to -1**	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24[o]**
Study Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**
Study Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit window (± days)	**0**		**0**	**1**	**2**	**7**	**7**	**7**	**7**	**7**	**7**
Anti-pegcetacoplan peptide and anti-PEG Ab assay [n]		~~X~~		X	~~X~~	~~X~~		~~X~~			X
Hematology		X		X	X	X	X	X	X	X	X
Serum chemistry		X		X	X	X	X	X	X	X	X
Coagulation profile [o]		X		X	X	X	X	X	X	X	X
TNFα, IL-6, IL-10, IFNγ and IL-1β		X		~~X~~	~~X~~	~~X~~	~~X~~	X	~~X~~	~~X~~	X
Complement profile (C3, functional assays for classical and alternative complement pathways)		X		~~X~~	~~X~~	~~X~~	~~X~~	X	~~X~~	~~X~~	X
Flow cytometry for C3 deposition on RBCs [p]	X			X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X
Ferritin, vitamin B_{12}/folate	X			X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X
Iron	X			X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X
DAT monospecific C3 and IgG	X			~~X~~	~~X~~	~~X~~	~~X~~	X	~~X~~	~~X~~	X
Immunoglobulins quantitative (IgG, IgM, and IgA) [q]	X					X			X		X
Serum cold agglutinin titer (at 4 °C) [q]	X					X			X		X
HIV, HCV-RNA, HBV-DNA	X										
EBV, *Mycoplasma pneumoniae*	X										

Table 5 Revised COVID-19 minimum schedule of assessments: Screening to Week 24 – Part A

Study Period	**Screening [a]**		**Part A: Double-blind treatment period**								
Study Week	**-4 to -1**	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24[o]**
Study Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**
Study Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit window (± days)	**0**		**0**	**1**	**2**	**7**	**7**	**7**	**7**	**7**	**7**
MYD88 Mutation Testing (only in patients requiring a bone marrow biopsy or if already done per local institution practice)	X										
Antinuclear antibodies	X										
Serum pregnancy (B-HCG and FSH)		X									
Urine pregnancy test [r]			X			X	X	X	X	X	X
FACT-An		X		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X
SF-12		X		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X
EQ-5D-5L		X		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X
Bone marrow biopsy for eligibility (as needed) [s]	X										
Adverse events		X	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X
Drug dispensation for home administration			X	X	X	X	X	X	X	X	X

Abbreviations: Ab, Antibody(ies); AE, Adverse event; B-HCG, Beta human chorionic gonadotropin; C3, Complement component 3; CAD, Cold agglutinin disease; DAT, Direct antiglobulin test; DNA, Deoxyribonucleic acid; EBV, Epstein-Barr virus; ECG, Electrocardiogram; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; FACT-An, Functional Assessment of Cancer Therapy-Anemia/Fatigue; FSH, Follicle-stimulating hormone; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; ICF, Informed consent form; IFNγ, Interferon-gamma; Ig, Immunoglobulin; ; IL, Interleukin; IMP, Investigational medicinal product; PEG, Polyethylene glycol; PK, Pharmacokinetic; RBC, Red blood cell; RNA, Ribonucleic acid; s.c., Subcutaneous; SF-12, 12-Item Short Form Survey; TNFα, Tumor necrosis factor-alpha; WOCBP, Women of childbearing potential.

[a] Screening period is up to 4 weeks before randomization, but certain assessments, including some laboratory assessments and quality of life questionnaires, are to be performed within 7 days before randomization.

[b] The status of vaccination against *Neisseria meningitidis* Types A, C, W, Y, and B, *Streptococcus pneumoniae*, and *Haemophilus influenzae* Type B should be confirmed and any required vaccinations or boosters are to be administered as described in Section 6.4.1.2.
[c] To receive treatment with IMP, patients who are documented nonresponders to vaccination or cannot be vaccinated prior to IMP initiation must receive prophylactic antibiotics according to local standard practices.
[d] Full physical examination will include assessment of the following items: general; head, ears, eyes, nose, and throat; dentition; thyroid (endocrine); heart; chest; lungs; abdomen; skin; extremities; back/neck; musculoskeletal system and lymph nodes.
[e] Brief physical examination will include general appearance, heart, lungs, abdomen and extremities.
[f] Both height and weight measurements should be done without shoes on. Height will be recorded at screening only.
[g] Patients will self-administer s.c. IMP, after receiving appropriate training by research personnel. Dosing diaries will be used for study treatment and are to be completed for each dose administered at the clinic or at home. IMP will be dosed at the clinical site on Day 1. On dosing days that coincide with clinic visits, doses will be administered at the clinic visit.
[h] Between site visits, patients will be instructed to report any infusion-site reaction to the investigator or other study personnel.
[i] On clinic dosing days, vital signs will be measured within 2 hours before dosing and venipuncture (and ECG, if applicable), and at 30 minutes (± 5 minutes) post dose. (see Section 6.5.4.4). All vital signs will be measured after the patient has been resting in a sitting position for at least 5 minutes, except when supine or semi-reclined because of study procedures and/or AEs or if deemed necessary by the investigator.
[k] Baseline laboratory assessments within 7 days before Day 1. If IMP is administered at study visit, blood samples will be taken before dosing.
[m] PK samples will be taken 15 minutes predose at each visit.
[n] For patients with positive anti-pegcetacoplan peptide or anti-PEG Ab in last dose sample, additional samples will be collected every 6 months from last dose until Ab levels returns to baseline.
[o] The use of silica reagents in coagulation panels should be avoided in all patients.
[p] If the baseline sampling is not performed at the screening visit, it will be collected at Visit 2 prior to dosing.
[q] Serum samples for immunoglobulins quantitative and CAD titer assessment to be kept at 37 ºC to 38 ºC (until serum has been removed from the clot, after which the sample can be handled at room temperature).
[r] Urine pregnancy test will be completed for WOCBP prior to dosing on days where dosing coincides with clinic visits. In case of COVID-19 restrictions, a home test will be used.
[s] Bone marrow biopsy only needed if biopsy not previously undertaken within 1 year prior to ICF signature.

Note: Unscheduled additional visits may be performed at the investigator's judgment. Any of the study procedures or other assessments may be performed at the unscheduled visit at the discretion of the investigator.

Table 6 Revised COVID-19 minimum schedule of assessments: Part B, Part C and Follow-up period

Study Period	**Part B: Open-label treatment period**			**Part C: Open-label maintenance period**					**Follow-up period [p]**	
									EOT/ET	**EOS**
Study Week	**32**	**40**	**48**	**56**	**64**	**72**	**80**	**88**	**96**	**104**
Study Day	**225**	**281**	**337**	**393**	**449**	**505**	**561**	**617**	**673**	**729**
Study Visit	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**21**
Visit window (± days)	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
RBC transfusions collection	X	X	X	X	X	X	X	X	X	X
Prophylactic antibiotic administration [a]	According to local standard practices in patients who cannot be vaccinated									
Full physical examination (including weight) [b]									X	X
Brief physical examination (including weight) [c]	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		
12-lead ECG *(prior to venipuncture)*	~~X~~								X	X
IMP administration [d]	Twice weekly----------→			Twice weekly----------→						
Infusion-site assessment [e]	X	X	X	X	X	X	X	X	X	
Concomitant medications/treatments	X	X	X	X	X	X	X	X	X	X
Vital sign measurements [f]	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Urine studies	X	X	X	X	X	X	X	X	X	X
Blood [g]	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics [h]			X						X	X
Anti-pegcetacoplan peptide and anti-PEG Ab assay [i]	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X	X
Hematology	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation profile [k]	X	X	X	X	X	X	X	X	X	X
TNFα, IL-6, IL-10, IFNγ and IL-1β	~~X~~	~~X~~	~~X~~						~~X~~	~~X~~

Table 6 Revised COVID-19 minimum schedule of assessments: Part B, Part C and Follow-up period

Study Period	Part B: Open-label treatment period			Part C: Open-label maintenance period					Follow-up period [p]	
									EOT/ET	EOS
Study Week	**32**	**40**	**48**	**56**	**64**	**72**	**80**	**88**	**96**	**104**
Study Day	**225**	**281**	**337**	**393**	**449**	**505**	**561**	**617**	**673**	**729**
Study Visit	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**21**
Visit window (± days)	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Complement profile (C3, functional assays for classical and alternative complement pathways)	~~X~~	~~X~~	~~X~~						X	X
Flow cytometry for C3 deposition on RBCs[m]	~~X~~	~~X~~	~~X~~						X	X
Ferritin, vitamin B_{12}/folate	~~X~~	~~X~~	~~X~~						X	X
Iron	~~X~~	~~X~~	~~X~~						X	X
DAT monospecific C3 and IgG	~~X~~	~~X~~	~~X~~						X	X
Immunoglobulins quantitative (IgG, IgM, and IgA) [n]			X						X	X
Serum cold agglutinin titer (at 4 °C) [n]			X						X	X
Urine pregnancy test (every 4 weeks) [o]	X	X	X	X	X	X	X	X	X	X
FACT-An	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
SF-12	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
EQ-5D-5L	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Adverse events and serious adverse events	X	X	X	X	X	X	X	X	X	X
Drug dispensation for home administration	X	X	X	X	X	X	X	X		

Abbreviations: Ab, Antibody(ies); C3, Complement component 3; CAD, Cold agglutinin disease; DAT, Direct antiglobulin test; ECG, Electrocardiogram; EOS, End of study; EOT, End of treatment; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; ET, Early termination; FACT-An, Functional Assessment of Cancer Therapy-Anemia/Fatigue; IFNγ, Interferon-gamma; Ig, Immunoglobulin; IL, Interleukin; IMP, Investigational medicinal product; PEG, Polyethylene glycol; PK, Pharmacokinetic; RBC, Red blood cell; s.c., Subcutaneous; SF-12, 12-Item Short Form Survey; TNFα, Tumor necrosis factor-alpha; WOCBP, Women of childbearing potential.

[a] To receive treatment with IMP, patients who are documented nonresponders to vaccination or cannot be vaccinated prior to IMP initiation must receive prophylactic antibiotics according to local standard practices.

[b] Full physical examination include assessment of the following items: general; head, ears, eyes, nose, and throat; dentition; thyroid (endocrine); heart; chest; lungs; abdomen; skin; extremities; back/neck; musculoskeletal system and lymph nodes. Weight will also be recorded at each physical examination.

[c] Brief physical examination will include general appearance, heart, lungs, abdomen and extremities. Weight will also be recorded at each physical examination.

[d] Patients will self-administer s.c. IMP, after receiving appropriate training by research personnel. Dosing diaries will be used for study treatment and are to be completed for each dose administered at the clinic or at home. On dosing days that coincide with clinic visits, doses will be administered at the clinic visit.

[e] Between site visits, patients will be instructed to report any infusion-site reaction to the study coordinator.

[f] On clinic dosing days, vital signs will be measured within 2 hours before dosing and venipuncture (and ECG, if applicable), and at 30 minutes (± 5 minutes) post dose. (see Section 6.5.4.4).

[g] If IMP is administered at study visit, blood samples will be taken before dosing.

[h] PK samples will be taken 15 minutes predose at each visit.

[i] For patients with positive anti-pegcetacoplan peptide or anti-PEG Ab in last dose samples, additional samples will be collected every 6 months from last dose until Ab levels returns to baseline.

[k] The use of silica reagents in coagulation panels should be avoided in all patients.

[m] If the baseline sampling is not performed at the screening visit, it will be collected at Visit 2 prior to dosing.

[n] Serum samples for immunoglobulins quantitative and CAD titer assessment to be kept at 37 ºC to 38 ºC (until serum has been removed from the clot, after which the sample can be handled at room temperature).

[o] Urine pregnancy test will be completed for WOCBP every 4 weeks, using a home test if there is no clinic visit. Urine pregnancy test to be performed prior to dosing on days where dosing coincides with clinic visits.

[p] After completion of the maintenance period, patients will complete an EOT visit. Patients who discontinue early should complete an ET visit. An EOS visit will be performed 8 weeks (± 7 days) after treatment discontinuation for any reason.

Note: Unscheduled additional visits may be performed at the investigator's judgment. Any of the study procedures or other assessments may be performed at the unscheduled visit at the discretion of the investigator.