CLINICAL STUDY REPORT

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)

Protocol Number:	Sobi.PEGCET-101
Investigational Medicinal Product:	Pegcetacoplan
Indication:	Cold Agglutinin Disease (CAD)
Phase:	Phase 3
Sponsor:	Swedish Orphan Biovitrum AB 112 76 Stockholm Sweden
Sponsor Representatives:	Luis López Lazaro, MD, PhD Medical Director Clinical Science Pegcetacoplan Johan Szamosi Statistical Science Director Swedish Orphan Biovitrum AB
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First Patient, First visit:	22 September 2022
Early Study Termination:	11 September 2024
Version; date:	Final v1.0; 28 March 2025

The study was conducted according to the protocol and in compliance with GCP, with the Declaration of Helsinki, and with other applicable regulatory requirements.

2. SYNOPSIS

Name of Company:	**Volume:**	(For national authority use only)
Name of Finished Product:	**Page:**	
Name of Active Ingredient(s):		

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)

Protocol Number: Sobi.PEGCET-101

Study Period: **Study Phase:** 3

Date of first patient, first visit: 22 September 2022

Date of last patient, last visit: 11 September 2024

The study was terminated early due to enrollment challenges arising from a decreased medical need for pegcetacoplan in CAD (i.e., limited number of patients available to participate in the study). Upon the decision to terminate the study, the patients who were ongoing were allowed to stay on treatment until 10 July 2024 to move out of the cold season and have appropriate time to transition to alternative treatment.

Study Centers: The study was conducted at 49 study centers in 15 countries.

Number of Patients (planned and analyzed): A total of 57 patients were planned to be enrolled in the study. Only 24 patients were enrolled due to the premature study termination and all enrolled patients were included in the analysis.

Publication(s): None at the time of writing this report.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary	
• To demonstrate the efficacy of twice weekly SC 1080 mg infusions of pegcetacoplan compared with that of placebo in patients with CAD	• Response to treatment at Week 24 Response is defined as: o An increase in Hb of ≥1.5 g/dL from Baseline or Hb normalization at Week 16; and o Maintenance of this effect from Week 16 to Week 24; and o The absence of PRBC transfusions (between Week 5 and Week 24) Note: Hb normalization is defined as within normal range (between the defined LLN and ULN), as set by the testing laboratory
Secondary	
Key secondary efficacy	
• 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	• 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

Other secondary efficacy	
• 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 describe long-term effect of pegcetacoplan in patients with CAD	<u>Secondary efficacy - Part A</u>: • Number of PRBC transfusions from Week 5 to Week 24 • Change from Baseline to Week 24 in the following: o LDH level o Haptoglobin level o Indirect bilirubin level o ARC o D-dimer level • Normalization of markers of hemolysis at Week 24, specifically: o LDH level o Indirect bilirubin level o ARC • Time to first normalization from Baseline to Week 24 for the following: o Hb level o LDH level o Indirect bilirubin level o ARC • Number of PRBC units transfused from Week 5 to Week 24 • Change from Baseline to Week 24 in the following: o FACIT-F subscale score of the FACT-An scale o SF-12 score o EQ-5D-5L score <u>Secondary efficacy - Part B:</u> • Change from Baseline to Week 48 in the following: o Hb level o LDH level o Haptoglobin level o Indirect bilirubin level o ARC o D-dimer level • Normalization of markers of hemolysis at Week 48, specifically: o LDH level o Indirect bilirubin level o 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:
	  o FACT-An score
	  o FACIT-F subscale score of the FACT-An scale
	  o SF-12 score
	  o EQ-5D-5L score
	
	<u>Tertiary efficacy - Part C</u>:
	• Change from Baseline to Week 96 in the following:
	  o Hb level
	  o LDH level
	  o Haptoglobin level
	  o Indirect bilirubin level
	  o ARC
	  o D-dimer level.
	• Normalization of markers of hemolysis at Week 96, specifically:
	  o LDH level
	  o Indirect bilirubin level
	  o ARC
	• Change from Baseline to Week 96 in the following:
	  o FACT-An score
	  o FACIT-F subscale score of the FACT-An scale
	  o SF-12 score
	  o EQ-5D-5L score

Safety	
• To assess tolerability, safety and immunogenicity of pegcetacoplan in patients with CAD	• AEs up to 8 weeks after EOT • SAEs up to 8 weeks after EOT • AEs leading to premature discontinuation of the IMP. • Clinically meaningful laboratory abnormalities up to 8 weeks after EOT • Changes from Baseline in laboratory parameters markers • 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

Ab=antibody; AE=adverse event; ARC=absolute reticulocyte count; CAD=Cold Agglutinin Disease; ECG=electrocardiogram; EOT=end of treatment; EQ-5D-5L=5-Level EuroQoL 5-Dimension score; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-An=Functional Assessment of Cancer Therapy-Anemia/Fatigue; Hb=hemoglobin; IMP=investigational medicinal product; LDH=lactate dehydrogenase; LLN=lower limits of normal; PRBC=packed red blood cells; SAE=serious adverse event; SC=subcutaneous; SF-12=12-Item Short Form survey; ULN=upper limits of normal.

Study Design:

This was a Phase 3, randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of pegcetacoplan 1080 mg , administered twice weekly by subcutaneous (SC) infusion in patients with CAD.

A total of 57 patients were planned to be enrolled; and randomized in a 2:1 ratio to receive either pegcetacoplan or placebo, respectively. The randomization was stratified by transfusion history (number of transfusions during the 6-month period prior to randomization ≥1; 0).

The planned length of participation in the study for each patient was a maximum of 110 weeks. The study comprised of 5 periods:

- Screening period: Up to 4 weeks (extended by up to 2 additional weeks when needed)
- Double-blind treatment period (Part A): 24 weeks
- Open-label treatment period (Part B): 24 weeks
- Open-label maintenance period (Part C): Up to additional 48 weeks or until the product was commercially available
- Follow-up period: 8 weeks

Screening period (up to 4 weeks; extended by up to 2 additional weeks):

Informed consent was obtained during this period prior to performing any study-related procedures. Patients with acute hemolytic crisis received blood cell transfusions during this period. The dosing was started at least 7 days after the last transfusion.

Patients were screened to confirm that the selection criteria for the study had been met. Key inclusion and exclusion criteria were reviewed by the study medical monitor and eligibility confirmed prior to the enrollment. When needed and after consultation with the medical monitor, the Screening period was extended by up to 2 additional weeks (e.g., eligibility laboratory results not available due to technical reasons or the patients received a red blood cells (RBCs) transfusion during the last week of the Screening period or reasonably reversible medical reasons such as coronavirus disease 2019 infection).

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

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

Patients were randomized into the study to receive SC pegcetacoplan or placebo (investigational medicinal product [IMP]) twice weekly for 24 weeks.

All standard of care medications could be continued, except for protocol-defined prohibited medications.

During this period, patients received a blood transfusion if hemoglobin (Hb) level was <7.0 g/dL. Transfusion in symptomatic patients with Hb levels ≥7.0 g/dL and <9.0 g/dL was considered during this period at the discretion of investigator.

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

All patients who completed the 24-week double-blind treatment period were eligible to enter the open-label treatment period where they received pegcetacoplan 1080 mg SC twice weekly for up to 24 weeks (Week 48).

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

After completion of the open-label treatment period, patients who benefited from therapy without significant side effects were to continue to receive pegcetacoplan 1080 mg SC twice weekly for a maximum of 48 additional weeks or until the product was commercially available, whichever occurred first. If the commercial product was not available at the end of Part C, patients were to be managed outside of the current study on a case-by-case basis, in accordance with applicable laws and regulations.

Follow-up period (8 weeks):

After completion of the open-label maintenance period, or when patients discontinued IMP treatment early, an end of treatment (EOT) or early termination (ET) visit was performed, followed by an end of study (EOS) visit 8 weeks later.

Diagnosis and Main Criteria for Inclusion:

1. Age 18 years or older
2. Diagnosis of primary CAD on the basis of the presence of **all** of the following criteria at Screening:
   a. Signs of hemolysis with abnormal values for at least 2 of the following hemolytic markers:
      i. Reduced haptoglobin level (<lower limit of normal [LLN])
      ii. Elevated lactate dehydrogenase (LDH) level (>upper limit of normal [ULN])
      iii. Elevated indirect bilirubin level (>ULN; >3 x ULN for patients with Gilbert-Meulengracht syndrome)
      iv. Increased absolute reticulocyte count (ARC; above the ULN)
   b. Monospecific direct antiglobulin test strongly positive for complement component (C3d)
   c. Cold agglutinin titer ≥64 at 4°C
3. Hemoglobin level ≤9 g/dL at Screening
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 had not received a bone marrow biopsy within 1 year of their Screening visit or for whom bone marrow biopsy reports were incomplete or unavailable, were required to receive a bone marrow biopsy to determine eligibility
6. Body weight ≤100 kg
7. Either had vaccination against *Streptococcus pneumoniae (S. pneumoniae)*, *Neisseria meningitidis (N. meningitidis*; Types A, C, W, Y, and B), and *Haemophilus influenzae (H. 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 IMP 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 IMP 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. This was not applicable for Japan as the *N. meningitidis* vaccine was not approved in Japan
   c. *S. pneumoniae*: PCV13 and/or 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 the IMP

   Vaccination was mandatory unless documented evidence existed that patients were non-responders to vaccination. Vaccinations were to be administered following the ACIP recommendations for adults or children with complement deficiencies and/or immunocompromising conditions

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

   Notes:

   a. Postmenopausal was defined as having had 12 consecutive months with no menses without an alternative medical cause
   b. Intravaginal, transdermal, injectable, or implantable forms of hormonal contraception methods were prohibited in Japan
9. Men had to 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

Test Product, Dose and Mode of Administration, and Lot Numbers: Pegcetacoplan, 1080 mg twice weekly, SC infusion (20 mL), Lot numbers: 2654-115, 2654-120, 2654-123, and 2654-126.

Reference Therapy, Dose and Mode of Administration, and Lot Numbers: Placebo, twice weekly, SC infusion, Lot numbers: 2556-107, 2556-108, 2556-109, and 2557-101.

Duration of Treatment: Up to 96 weeks (Part A – 24 weeks; Part B – 24 weeks (up to Week 48); Part C – up to 48 weeks [up to Week 96])

The study was prematurely terminated on 11 September 2024. At the time of decision to terminate the study (10 January 2024), all the patients who were ongoing were allowed to stay on treatment until 10 July 2024 to move out of the cold season and have appropriate time to transition to alternative treatment.

Criteria for Evaluation:

Efficacy:

Efficacy was assessed by:

- Hb level and other clinical laboratory markers of hemolysis (lactate dehydrogenase [LDH], haptoglobin, indirect bilirubin, ARC, D-dimer)
- Packed red blood cell (PRBC) transfusions (receipt and avoidance as well as number of units from Week 5 to Week 24)
- Health-related quality of life:
  - Functional Assessment of Cancer Therapy-Anemia/Fatigue (FACT-An) score
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale score
  - 12-Item Short Form survey (SF-12) score
  - EuroQoL 5-Dimension (EQ-5D-5L) score

Safety:

Safety was assessed through the incidence of adverse events (AEs), laboratory assessments, physical examination, anti-pegcetacoplan peptide antibody and anti-polyethylene glycol (anti-PEG) antibody assessments, vital signs, electrocardiogram (ECG), and infusion-site reactions/pump-safety assessments.

Statistical Methods:

Efficacy:

All efficacy endpoints were to be analyzed using the intent-to-treat (ITT) set, defined as all randomized patients.

Primary Endpoint:

The primary efficacy endpoint was response to treatment at Week 24, defined as an increase in Hb level of ≥1.5 g/dL from Baseline or Hb normalization (as defined by testing laboratory) at Week 16, maintenance of this effect from Week 16 to Week 24, and the absence of PRBC transfusions (between Week 5 and Week 24). The number and percentage of patients who responded were tabulated by treatment group and compared between treatment groups using an exact Cochran-Mantel-Haenszel (CMH) test stratified for the following criterion (≥ 1 / 0 transfusions during the 6-month period prior to randomization). Refer to the statistical analysis plan (SAP) for details on the supportive and subgroup analyses.

Secondary Endpoints:

Key Secondary Endpoints:

The change from Baseline to Week 24 in Hb was analyzed using a 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 was estimated for each visit, along with its 95% confidence interval (CI) and p-value.

Transfusion avoidance (Yes/No) from Week 5 to Week 24 was tabulated by treatment group and compared between treatment groups using an exact CMH test.

The change from Baseline at Week 24 in the FACT-An scores was analyzed using a MMRM.

To preserve the Type 1 error, a fixed-sequence testing strategy was used; hence, statistical significance of the first key secondary endpoint analysis was only concluded if statistical significance was achieved with the analysis of the primary endpoint. Statistical significance of the second key secondary endpoint analysis was only concluded if statistical significance was achieved on the first key secondary endpoint analysis and so on. Refer to the SAP for details on the subgroup analyses.

Other Secondary Endpoints:

Part A:

The number of PRBC transfusions from Week 5 to Week 24 in each treatment group was compared using a stratified Wilcoxon rank-sum test.

The change from Baseline at Week 24 in LDH, haptoglobin, indirect bilirubin, ARC, and D-dimer was analyzed using MMRM analysis, using an unstructured covariance matrix and the Kenward-Roger method for calculating the degrees of freedom.

The normalization of markers of hemolysis (LDH, indirect bilirubin, and ARC), at Week 24 was analyzed by tabulating the number and percentage of patients who responded by treatment group and compared between treatment groups using an exact CMH test. Kaplan-Meier plots were 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. Median survival estimates were provided.

The number of units of PRBCs transfused from Week 5 to Week 24 in each treatment group was compared using a stratified Wilcoxon rank-sum test.

The change from Baseline at Week 24 in FACIT-F subscale score of the FACT-An scale, SF-12 (Physical and Mental Component Scores [PCS and MCS, respectively]), and EQ-5D-5L were analyzed using MMRM. Summary statistics by treatment group were presented at each assessment visit during the 24-week double-blind treatment period.

Part B:

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

The change from Baseline at Week 48 in FACT-An, SF-12, EQ-5D-5L, and FACIT-F subscale score of the FACT-An scale was analyzed using descriptive statistics.

Exploratory endpoints:

All exploratory endpoints were summarized descriptively. Refer to SAP for more details on the exploratory endpoint analyses.

Safety and tolerability:

All safety analyses were carried out descriptively on the Safety set, consisting of all patients who received at least 1 dose of the IMP. The evaluation of safety and tolerability was carried out separately for the double-blind placebo-controlled period and the open-label period. Other analyses are detailed in the SAP.

All AEs were coded using the Medical Dictionary for Regulatory Activities, version 27.1, September 2024. Treatment-emergent adverse events (TEAEs) were summarized by system organ class (SOC) and preferred term (PT), treatment group for number of patients and proportion reporting the event. A similar summary was produced for treatment-emergent serious adverse events (TESAEs), TEAEs leading to premature discontinuation of the IMP, and AEs related to the IMP. The intensity of TEAEs and the relationship to the IMP was summarized for each SOC and PT by treatment group. TEAEs that led to IMP discontinuation were summarized by frequency tables. The AE summaries were presented across all patients. All AEs were listed by patient, along with information regarding onset, duration, relationship to IMP, relationship to device, severity, action taken with the IMP, treatment of event, and outcome.

The results of laboratory assessments, vital signs, and ECGs were summarized by treatment group using descriptive statistics. The changes from Baseline in clinical laboratory test results were summarized using descriptive statistics.

Laboratory data were graded for severity using Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and all Grade ≥3 results were considered clinically meaningful. Changes in physical examinations were described in a data listing.

***Immunogenicity*:**

Frequency tables were presented to summarize the presence of anti-drug antibody (ADA) to PEG moiety and to pegcetacoplan peptide. In ADA, evaluable patients were defined as:

- Baseline ADA: having at least one evaluable ADA sample at Baseline.
- Treatment-emergent ADA (TEADA) and treatment-boosted ADA (TBADA): having at least one evaluable ADA sample at Baseline and at least one evaluable post dose sample.

Summary tables for ADA were presented for pegcetacoplan peptide and PEG. Neutralizing antibodies (NAb) were also presented for antibodies to pegcetacoplan peptide. Spaghetti plots of individual ADA titers were presented for pegcetacoplan peptide and PEG in semi-logarithmic format. All immunogenicity data were presented in a listing.

Interim analysis:

No interim analyses were conducted for this study.

Patient Characteristics:

Patients initially assigned to pegcetacoplan and to placebo had overall comparable demographic characteristics. No patients with childbearing potential were included in the study. As expected from the general characteristics of the CAD patient population, most study patients were elderly with a median age at study entry of 73.5 years and ages ranging from 59 to 84 years.

Patients targeted medical history was overall comparable, other than for

- a marginally higher proportion of patients in the pegcetacoplan group with reduced haptoglobin or prior hospitalization due to CAD.
- a higher proportion of patients in the pegcetacoplan group with elevated indirect bilirubin or noticeable symptoms.
- a higher proportion of patients who have received prior rituximab-based treatment in the placebo group (7/8 or 87.5%) as compared to the pegcetacoplan group (7/16 or 43.8%).
- Some single patient findings also differed.

Efficacy Results:

The study's primary endpoint was not met. At Week 24, 8/16 patients (50.0%) treated with pegcetacoplan achieved a response (as defined in the primary endpoint), compared with 2/8 patients (25.0%) treated with placebo. No statistically significant difference was observed in the response rates between the two groups (p-value=0.262). Failure to meet the primary endpoint might have been related to the premature discontinuation of the study, leading to an insufficient sample size.

Key secondary endpoints

Because the primary endpoint was not met, formal statistical testing for key secondary endpoints was not allowed.

- The mean (SD) change in Hb levels from Baseline to Week 24 was 2.8 g/dL (1.9) in the pegcetacoplan group and 1.5 g/dL (1.1) in the placebo group. The difference in the least squares (LS) Mean change from Baseline between the two treatment groups was 1.5 g/dL (95% CI=0.65, 2.33), thereby suggesting an improvement in Hb levels from Baseline to Week 24 in the pegcetacoplan group compared with placebo.
- At Week 24, there were no major differences in proportion of patients achieving transfusion avoidance in the pegcetacoplan group (12/16 patients [75.0%]) compared to the placebo group (5/8 patients [62.5%]).
- Patients receiving pegcetacoplan showed slightly greater improvement in the FACT-An total scores at Week 24. The mean subscores for physical and functional components improved by Week 24, with a slightly higher mean (SD) change reported with pegcetacoplan than placebo.

Other secondary endpoints

- Seven of 16 patients (43.8%) in the pegcetacoplan group achieved Hb normalization and none of the 8 patients in the placebo group achieved Hb normalization during the first 24 weeks of the study.
- The mean (SD) number of PRBC units transfused from Week 5 to Week 24 was 1.5 (3.6) in the pegcetacoplan group and 1.1 (2.8) in the placebo group.
- Both pegcetacoplan and placebo groups exhibited a reduction in LDH levels from Baseline to Week 24, with a mean (SD) change from Baseline of -251.7 U/L (211.3) and -82.0 U/L (138.5), respectively. A greater reduction in LDH levels by Week 24 was noted with pegcetacoplan. Five of 13 patients (38.5%) in the pegcetacoplan group and 1/8 patient (12.5%) in the placebo group achieved normalization in LDH levels at Week 24. The difference (95% CI) in normalization rate between the groups was 0.268 (-0.064, 0.601).
- The mean (SD) change in haptoglobin concentrations from Baseline to Week 24 was 0.3 g/L (0.5) in the pegcetacoplan group and 0.01 g/L (0.02) in the placebo group. In addition, 4/15 patients (26.7%) who had abnormal haptoglobin results at Baseline in the pegcetacoplan group achieved normalization at Week 24 as compared to 0/6 on placebo. The difference in the normalization rate (95% CI) between pegcetacoplan and placebo was 0.274 (0.049, 0.499), suggesting a meaningful difference between the two groups.
- The pegcetacoplan group showed a decrease in the indirect bilirubin levels from Baseline to Week 24, by a mean (SD) change of -31.6 µmol/L (23.3). In the patients who received placebo, the indirect bilirubin levels slightly increased, with a mean (SD) change from Baseline to Week 24 of 8.2 µmol/L (19.3). In addition, of

13 patients in the pegcetacoplan group who had abnormal indirect bilirubin levels at Baseline, 9 patients (69.2%) achieved normalization at Week 24. Of 6 patients in the placebo group whose indirect bilirubin levels were abnormal at Baseline, 1 patient (16.7%) achieved normalization at Week 24. The difference (95% CI) in normalization rates between the two groups was 0.520 (0.131, 0.910).

- The ARC levels decreased in both groups between Baseline and Week 24, with mean (SD) changes from Baseline of -41.2 × 10^9/L (62.4) in the pegcetacoplan group and -38.0 × 10^9/L (19.9) in the placebo group. The LS Mean (SE) difference in change from Baseline between the two treatment groups was -20.7 × 10^9/L (16.0). At Baseline, 10 patients in the pegcetacoplan group and 8 patients in the placebo group had abnormal ARC levels. Of these, 4 patients (40.0%) treated with pegcetacoplan and 2 patients (25.0%) treated with placebo achieved normalization at Week 24. The difference (95% CI) in the normalization rate between the two groups was 0.114 (-0.290, 0.517).
- At Baseline, the D-dimer levels were lower in the pegcetacoplan group (mean [SD]=1108.4 µg/L FEU [863.1]) as compared to the placebo group (mean [SD]=2531.8 µg/L FEU [3823.4]). At Week 24, the placebo group showed a greater reduction (improvement) in D-dimer levels, when compared with the pegcetacoplan group. The mean (SD) change from Baseline was -698.7 µg/L FEU (927.5) and -1722.8 µg/L FEU (3089.2) in the pegcetacoplan and placebo groups, respectively
- The mean changes from Baseline to Week 24 in the FACIT-F subscale, SF-12, and EQ-5D-5L scores demonstrated a minimal change from Baseline, consistent with better improvement in pegcetacoplan group in all measures, except EQ-5D-5L self-care (no change from Baseline).

Week 48 endpoints

By Week 48, the majority of patients had discontinued from the study; hence, it was not possible to meaningfully evaluate the efficacy results at Week 48.

Safety Results:

- Due to the early termination of the study, no Week 96 assessments were performed.
- A total of 20/23 pegcetacoplan-treated patients (87.0%) reported TEAEs, with all patients experiencing TEAEs during Part A. Majority of the TEAEs were of mild severity.
- A total of 7/23 patients (30.4%) treated with pegcetacoplan in Parts A, B, and C reported at least one TEAE related to the IMP. No related TEAEs of the same PT were reported in more than 1 patient.
- Overall, 18 TESAEs were reported in 10/23 patients (43.5%) while treated with pegcetacoplan during the study, with the highest incidence observed in the pegcetacoplan group during Part A (5/16 patients [31.3%]). Only one TESAE of COVID-19 infection was reported in the placebo group of Part A.
- One patient (4.3%) from Part A – pegcetacoplan group died due to a TESAE of Cholecystitis (severe and considered as not related to pegcetacoplan).
- The most commonly reported TEAEs by SOC were General disorders and administration site conditions, Infections and infestations, and Blood and lymphatic disorders. The most frequently reported TEAEs by PT that occurred in Part A during or within 8 weeks of treatment with pegcetacoplan included Fatigue, Oedema peripheral, COVID-19, Upper respiratory tract infection, and Cold type haemolytic anaemia.
- Ten TEAEs led to premature discontinuation of pegcetacoplan in 3/23 patients (13.0%; 2 patients from Part A – pegcetacoplan group and 1 patient from Parts B and C – previously treated with pegcetacoplan in Part A). The TEAEs that led to the discontinuation of IMP in Part A included Atrial fibrillation, Cardiac failure, Cholecystitis, Haemolytic anaemia, Pleural effusion, Pneumonia, Respiratory failure, and Scrotal oedema. One patient from Parts B and C, who had received pegcetacoplan in Part A, was discontinued from the study treatment due to the event of Cold type haemolytic anaemia. No treatment discontinuations occurred in the placebo group.

- The overall incidence of TEAESI was higher in pegcetacoplan-treated patients (78.3%) compared with placebo (50.0%). Six injection site TEAEs were reported in 4/16 patients (25.0%) receiving pegcetacoplan in Part A compared with 0/8 patients (0%) receiving placebo, Injection site TEAEs included Haemorrhage subcutaneous, Induration, Injection site mass, Injection site paraesthesia, Injection site pruritus, and Injection site swelling. All these events were considered to be related to pegcetacoplan, except for Injection site swelling. The proportion of patients reporting TEAEs within the SOC of infections was equal in both arms during Part A (50.0%), with the only identified infection by encapsulated bacteria (Enterococcal sepsis, also a TESAE and was considered as not related to the IMP by the investigator and sponsor) occurring in the pegcetacoplan arm. Infections, especially respiratory tract infections, were common in both treatment groups, with a higher incidence observed in patients treated with pegcetacoplan.
- Most of the changes from Baseline in hematology parameters, except for Hb that improved in the pegcetacoplan arm and ARC that improved in both treatment arms, were small and non-clinically meaningful. The TEAEs of abnormal hematological parameters included Cold type acute haemolytic anaemia, Haemolytic anaemia, Anaemia, Autoimmune haemolytic anaemia, and Warm autoimmune haemolytic anaemia, Thrombocytopenia, and Platelet count increased.
- No clinically meaningful changes in the serum chemistry (other than decreases in LDH and in the pegcetacoplan group on indirect bilirubin and increases in haptoglobin in CAD group potentially related to CAD improvement) and urinalysis values were identified during the study. Two TEAEs of Hypoglycaemia and Gamma-glutamyl transferase increased were recorded in Part A – Hypoglycaemia in the pegcetacoplan group, Gamma-glutamyl transferase increased in the placebo group. These TEAEs were of mild severity and recovered/resolved. The TEAE of Hypoglycaemia was considered as not related to the IMP, while the TEAE of Gamma-glutamyl transferase increased was considered as related to the IMP. No TEAEs related to abnormal urinalysis were reported.
- Two TEAEs related to coagulation panel were identified; Thrombin-antithrombin III complex increased in pegcetacoplan group of Part A and TEAE of Hypoprothrombinaemia in Parts B and C – previously on placebo. Both TEAEs were of mild in severity, recovered/resolved, and were considered as not related to the IMP. The coagulation test results were comparable between the two groups.
- No ADAs to pegcetacoplan peptide moiety were observed at Baseline. TEADAs incidence was 18.8% (3/16 patients) in Part A - pegcetacoplan group and 12.5% (1/8 patient) in patients initially on placebo, but TEADAs were found when the patient had already started treatment with pegcetacoplan. The overall incidence of ADA remained relatively low and NAb were found in a single sample.
- The ADA to PEG were common at Baseline, the incidence of TEADA and TBADA was relatively low, and the majority of TEADA cases were transient.
- Three TEAEs of abnormal vital sign parameters were recorded, including Hypotension (moderate), Pyrexia (mild), and Hypertension (mild). One clinically meaningful abnormal vital sign observation was made in association with a TEAE of Haemolysis.
- No clinically relevant abnormal findings were noted in the ECGs. Two TEAEs of Atrial fibrillation occurred in 2 patients, 1 patient from Part A – pegcetacoplan group and other from Parts B and C (received pegcetacoplan during Part A). Both TEAEs were moderate in severity and considered not related to the IMP.

Conclusions:

Mean changes from Baseline in Hb levels and other markers of hemolysis suggest that patients treated with pegcetacoplan exhibited a slightly better treatment response compared to those receiving placebo. However, since the primary and key secondary efficacy endpoints of this study were not met, no firm conclusions on the efficacy of pegcetacoplan in patients with CAD can be drawn. The small sample size due to the premature study termination, particularly in the placebo group, made comparisons between pegcetacoplan and placebo difficult.

The safety findings observed with pegcetacoplan in this study are in agreement with the established safety profile and anticipated safety outcomes within this elderly CAD population.

Version, date of report: Final v1.0, 28 March 2025

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

Abbreviation	Definition
Ab	Antibodies
ACIP	Advisory Committee on Immunization Practices
ADA	Anti-drug antibody
AIHA	Autoimmune hemolytic anemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ARC	Absolute reticulocyte count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below limit of quantification
BMI	Body mass index
BUN	Blood urea nitrogen
C	Complement component
C3d	Complement component 3d
CAD	Cold Agglutinin Disease
CI	Confidence interval
CKD	Chronic kidney disease
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CRA	Clinical Research Associate
CTCAE	Common Terminology Criteria for Adverse Events
DAT	Direct antiglobulin test
DNA	Deoxyribonucleic acid
EAIR	Exposure Adjusted Incidence Rate
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay

Abbreviation	Definition
EOS	End of study
EOT	End of treatment
EQ-5D-5L	5-Level EuroQol 5-Dimension
ET	Early termination
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-An	Functional Assessment of Cancer Therapy-Anemia/Fatigue score
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
H. influenzae	*Haemophilus influenzae*
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IFNγ	Interferon-gamma
Ig	Immunoglobulin
IL	Interleukin
IL-1β	Interleukin 1-beta
IL-6	Interleukin-6
IL-10	Interleukin-10
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LS Mean	Least squares mean
Max	Maximum

Abbreviation	Definition
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MCS	Mental component score
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MSD	Meso Scale Discovery
NA	Not applicable
NAb	Neutralizing antibody
N. meningitidis	*Neisseria meningitidis*
PCS	Physical component score
PD	Pharmacodynamics
PEG	Polyethylene glycol
pH	Potential of hydrogen
PK	Pharmacokinetics
PPS	Per-protocol set
PRBC	Packed red blood cell
PT	Preferred term
RBC	Red blood cells
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-12	12-Item Short Form survey
S. pneumoniae	*Streptococcus pneumoniae*
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBADA	Treatment-boosted anti-drug antibodies
TEADA	Treatment-emergent anti-drug antibody

Abbreviation	Definition
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TESAE	Treatment-emergent serious adverse event
TNFα	Tumor necrosis factor-alpha
UK	United Kingdom
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

5. ETHICS

5.1. Ethics Committee or Institutional Review Board

In accordance with regulatory requirements, copies of the protocol, amendments, and written informed consent form (ICF) were reviewed and approved by the governing institutional review board (IRB) and independent ethics committee (IEC) of each investigational center prior to the start of the study at that center. Information about the IRBs and IECs is provided in Appendix 16.1.3.

5.2. Ethical Conduct of the Study

This study was designed and monitored in accordance with the contract research organization's (CRO's) standard operating procedures, which complied with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki 2013 (WMA 1964-2013).

5.3. Patient Information and Consent

In accordance with regulations, written informed consent was obtained from all patients. The investigator had both ethical and legal responsibility to ensure that each individual being considered for inclusion in this study was given a full explanation of the protocol. Informed consent was obtained and documented during a Screening visit prior to initiation of any procedures that were performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). All patients received copies of their signed and dated ICFs.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was planned to be conducted in 57 patients at 49 study centers in 15 countries.

All aspects of the study were managed by Sobi and the CRO (Allucent). The responsibilities of Allucent as CRO included project management, clinical conduct, medical monitoring, clinical monitoring, maintenance of the Trial Master File, data management, biostatistics, and medical writing. The CROs in Japan and Norway are CMIC and Link Medical Research AS, respectively. Both these local CROs are Allucent vendors contracted to perform monitoring and regulatory activities in the respective regions. LabCorp is the central lab used to perform Flow Cytometry of C3 samples. Clinical laboratory, bioanalytical, and study medication supply services were used, as listed below. A list of investigators and other important personnel is provided in Appendix 16.1.4.

CRO	Allucent 2000 Centregreen Way, Suite 300 Cary, NC 27513 USA
Local CRO in Japan	CMIC Hamamatsucho Building 17F 1-1-1 Shibaura, Minato-ku Tokyo, 105-0023 Japan
Local CRO in Norway	Link Medical Research AS Gjerdrums vei 19, 0484 Oslo Norway
Central laboratory	ACM Global Laboratories 23 Hospital Fields Road/York, YO10 4DZ, UK
Regional/country central clinical laboratories	• ACM Medical Laboratory 150 Elmgrove Park Rochester, NY, 14624, USA • ACM Global Central Laboratory Singapore 1l Changi North Street 1 #04-05/09 Changi North Industrial Estate Singapore 498823
Bioanalytical laboratories:	• BioAgilytix 2300 Englert Drive Durham, MC 27713, USA • Exsera BioLabs Rm M20-3209, 1775 Aurora Court

	Aurora, CO 80045, USA • AIT Bioscience/Q2 7840 Innovation Blvd Indianapolis, Indiana 46278, USA • Labcorp CLS 8211 Scicor Drive Indianapolis, IN 46214-2985, USA • Labcorp CLS Singapore 1 International Business Park The Synergy, #04-14 Singapore 609917 • Labcorp Central Laboratory Services, S.à.r.l. Rue Moïse-Marcinhes 7 1217 Meyrin, Geneva Switzerland
Drug packaging, labelling, and distribution:	Almac Clinical Services United States of America
Almac depots used	• ACS NC (applicable for USA and Canada) 4204 Technology Drive, Durham, NC 27704 USA • ACS CR (applicable for Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Georgia, Germany, Hungary, Italy, Netherlands, Norway, Spain, UK) 9 Charlestown Road, Seagoe Industrial Estate Craigavon BT63 5PW Northern Ireland • D37-World Courier K.K. (applicable for Japan) Prologis Park Tokyo-Shinkiba 303-305 1-12-10 Shinkiba Koto-ku, Tokyo, Japan Zip code: 136-0082
Review and translation of label	Allucent

7. INTRODUCTION

7.1. Background Information

Autoimmune hemolytic anemia (AIHA) is defined as the increased destruction of red blood cells (RBCs) in the presence of anti-RBC autoantibodies, with or without complement activation (Barcellini 2015). AIHAs consist of warm-, cold-, and mixed-reactive antibody 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) (Swiecicki 2013).

Primary chronic cold agglutinin disease (CAD) is an uncommon form of AIHA in which hemolysis is thought to be entirely complement-dependent. Cold agglutinin disease 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°C (Berentsen 2016). The disease occurs most frequently in elderly patients, with a mean age at diagnosis of 68 years (Berentsen 2020).

Cold antibodies (immunoglobulin [Ig] M) temporarily bind to the RBC membrane, which in turn activates complement, and leads to the deposition of complement component (C3b) on the cell surface. These complement component (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 C9b 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 (Berentsen 2017). However, a substantial unmet medical need still existed at the time the study was designed.

In the meantime, another complement inhibitor was approved for CAD, sutimlimab. Sutimlimab was approved in April 2022 in the USA and in November 2022 in the European Union. Sutimlimab (formerly BIVV009) is a humanized IgG4 monoclonal antibody designed to target C1s, which is responsible for activating the classic complement pathway. Sutimlimab has been shown to result in a comparatively better efficacy as compared to placebo in patients with CAD who had not received transfusions in the prior 6 months, with improvement in a composite endpoint including hemoglobin (Hb) increase, transfusion avoidance, and lack of need for prohibited CAD medications, as well as in other endpoints such as Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score (CADENZA study) (Roth 2022). Sutimlimab was also reported to increase Hb and result in 71% transfusion avoidance over 26 weeks in patients who had received transfusions in the prior 6 months (CARDINAL study) (Roth 2021). Due to the approval of sutimlimab, the medical need for pegcetacoplan in the CAD indication greatly decreased.

Clinical data from studies with pegcetacoplan in patients with paroxysmal nocturnal hemoglobinuria indicated that pegcetacoplan was an effective complement-modulating agent that resulted in broad control of intravascular and extravascular hemolysis. A prospective pilot study of pegcetacoplan in patients with a primary diagnosis of warm AIHA or CAD in parallel showed consistent, meaningful, and prolonged effects of pegcetacoplan on most relevant clinical efficacy measures along with an acceptable safety profile (APL2-CP-AIHA-208 2020). Available safety

data from completed and ongoing clinical studies did not indicate any serious safety concern in patients treated with pegcetacoplan.

7.2. Rationale

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

Pegcetacoplan rapidly increased Hb values in 10 patients with CAD treated in a previous Phase 2 APL2-CP-AIHA-208 study, by reducing both intravascular and extravascular hemolysis (as shown by reduction and normalization of lactate dehydrogenase [LDH], indirect bilirubin, and absolute reticulocyte count [ARC]). Pegcetacoplan treatment led to transfusion independence in the majority of patients, while being well tolerated.

Thus, this Phase 3 study was conducted to confirm the safety and efficacy of pegcetacoplan in patients with CAD. Pegcetacoplan was compared to placebo in a double-blinded, randomized fashion. The treatment duration was 24 weeks for both treatment groups to ensure capturing a durable treatment effect. At the end of the randomized portion of the study, all ongoing patients were offered a 24-week treatment with pegcetacoplan in an open-label fashion, and 48 additional weeks to allow treatment continuity until the product would be commercially available.

The study was terminated early due to enrollment challenges arising from a decreased medical need for pegcetacoplan in CAD (i.e., limited number of patients available to participate in the study). Upon the decision to terminate the study (10 January 2024), the patients who were ongoing were allowed to stay on treatment until 10 July 2024 to move out of the cold season and have appropriate time to transition to alternative treatment.

8. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of twice-weekly SC 1080 mg infusions of pegcetacoplan compared with that of placebo in patients with CAD	• Response to treatment at Week 24 Response is defined as: o An increase in Hb of ≥1.5 g/dL from Baseline or Hb normalization at Week 16; and o Maintenance of this effect from Week 16 to Week 24; and o The absence of PRBC transfusions (between Week 5 and Week 24) Note: Hb normalization is defined as within normal range (between the defined LLN and ULN) respectively, as set by the testing laboratory.
Secondary	
Key secondary efficacy	
• 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	• 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
Other secondary efficacy	
• 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 describe long-term effect of pegcetacoplan in patients with CAD	<u>Secondary efficacy:</u> <u>Part A</u>: • Number of PRBC transfusions from Week 5 to Week 24 • Change from Baseline to Week 24 in the following: o LDH level o Haptoglobin level o Indirect bilirubin level o ARC o D-dimer level

Objectives	Endpoints
	• Normalization of markers of hemolysis at Week 24, specifically: o LDH level o Indirect bilirubin level o ARC • Time to first normalization from Baseline to Week 24 for the following: o Hb level o LDH level o Indirect bilirubin level o ARC • Number of PRBC units transfused from Week 5 to Week 24 • Change from Baseline to Week 24 in the following: o FACIT-F subscale score of the FACT-An scale o SF-12 score o EQ-5D-5L score <u>Part B</u>: • Change from Baseline to Week 48 in the following: o Hb level o LDH level o Haptoglobin level o Indirect bilirubin level o ARC o D-dimer level

	• Normalization of markers of hemolysis at Week 48, specifically:
	  o LDH level
	  o Indirect bilirubin level
	  o 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:
	  o FACT-An score
	  o FACIT-F subscale score of the FACT-An scale
	  o SF-12 score
	  o EQ-5D-5L score
	
	<u>Tertiary efficacy</u>:
	<u>Part C</u>:
	• Change from Baseline to Week 96 in the following:
	  o Hb level
	  o LDH level
	  o Haptoglobin level
	  o Indirect bilirubin level
	  o ARC
	  o D-dimer level.
	• Normalization of markers of hemolysis at Week 96, specifically:
	  o LDH level
	  o Indirect bilirubin level
	  o ARC
	• Change from Baseline to Week 96 in the following:
	  o FACT-An score
	  o FACIT-F subscale score of the FACT-An scale
	  o SF-12 score
	  o EQ-5D-5L score

Objectives	Endpoints
Safety	
• To assess tolerability, safety and immunogenicity of pegcetacoplan in patients with CAD	• AEs up to 8 weeks after EOT • SAEs up to 8 weeks after EOT • AEs leading to premature discontinuation of the IMP • Clinically meaningful laboratory abnormalities up to 8 weeks after EOT • Changes from Baseline in laboratory parameters markers • 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
Exploratory	
• To evaluate the PK of pegcetacoplan following twice-weekly SC infusions • To evaluate the effect of pegcetacoplan on complement biomarkers and pro-inflammatory cytokines	• Pegcetacoplan trough 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

Ab=antibody; AE=adverse event; ARC=absolute reticulocyte count; C3=complement component 3; CAD=Cold Agglutinin Disease; ECG=electrocardiogram; EOT=end of treatment; EQ-5D-5L=5-level EuroQoL 5-Dimension score; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-An=Functional Assessment of Cancer Therapy-Anemia/Fatigue; Hb=hemoglobin; IFNγ=interferon-gamma; IL=1β=interleukin 1-beta; IL-6=interleukin 6; IL-10=interleukin 10; LDH=lactate dehydrogenase; LLN=lower limits of normal; PK=pharmacokinetics; PRBC=packed red blood cells; RBC=red blood cells; SAE=serious adverse event;

SC=subcutaneous; SF-12=12-item Short Form survey; TNFα=tumor necrosis factor-alpha; ULN=upper limits of normal.

Note: Due to the premature termination of the study, Week 96 assessments were not performed, and its endpoints were not analyzed. The changes from the planned analyses are described in the Section 9.8.2.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design

9.1.1. Study Design

This was a Phase 3, randomized, double-blind, placebo-controlled multicenter study of pegcetacoplan 1080 mg or placebo, administered twice weekly by subcutaneous (SC) infusion in patients with CAD.

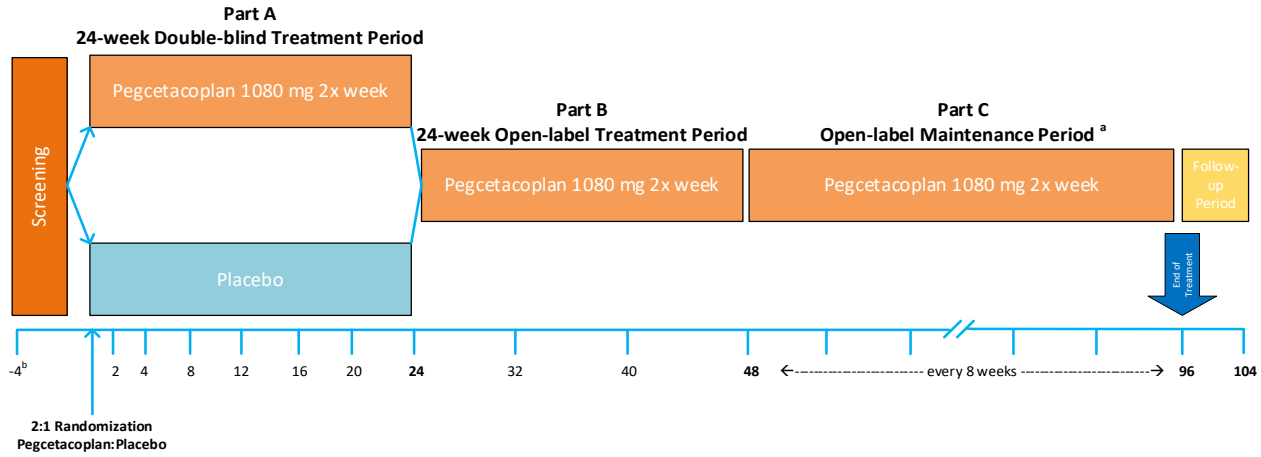
A total of 57 patients with CAD were planned to be enrolled and randomized in a 2:1 ratio to receive either pegcetacoplan or placebo. The randomization was stratified by transfusion history (number of transfusions during the 6-month period prior to randomization ≥1; 0).

The planned study duration for each patient was up to 110 weeks. The study was comprised of 5 periods:

- Screening period: Up to 4 weeks (extended by up to 2 additional weeks when needed)
- Double-blind treatment period (Part A): 24 weeks
- Open-label treatment period (Part B): 24 weeks
- Open-label maintenance period (Part C): Up to additional 48 weeks or until the product was commercially available
- Follow-up period: 8 weeks

The study design is outlined in Figure 9-1 and the visit schedule and planned assessments at each visit are detailed in the Protocol Table 1 and Table 2 (Appendix 16.1.1).

Figure 9-1. Study Design



Source: Protocol Figure 1 Study design.

a. Open-label maintenance for a maximum of 48 weeks or until the product was commercially available, whichever occurred first. If the commercial product was not available by the end of Part C, patients were to be managed outside of the current study on a case-by-case basis, in accordance with applicable laws and regulations.

b. When needed and after consultation with the medical monitor, the Screening period was extended by up to 2 additional weeks.

9.1.2. Screening Period (up to 4 weeks; extended by up to 2 additional weeks as needed)

Informed consent was obtained during a Screening visit before any study-related procedures were conducted. Patients experiencing acute hemolytic crisis may have received blood cell transfusions during the Screening period. The dosing was started at least 7 days after receiving the last transfusion.

Patients were screened to confirm that entry criteria for the study were met. Key inclusion and exclusion criteria were reviewed by the study medical monitor and eligibility was confirmed prior to the enrollment. As needed and after consultation with the medical monitor, the Screening period was extended by up to 2 additional weeks (e.g., when eligibility laboratory results were not available due to technical reasons or the patients received an RBC transfusion during the last week of the Screening period, or due to reasonably reversible medical reasons such as coronavirus disease 2019 [COVID-19] infection).

9.1.2.1. Retesting and Rescreening

Patients who failed to qualify for the study based on certain laboratory parameters were retested and/or rescreened at the discretion of the investigator.

9.1.2.1.1. Retesting

Retesting was defined as repeating laboratory tests within the same Screening period.

Retesting was allowed due to technical issues (e.g., hemolysis, clotting, etc.). Patients who initially failed to qualify for the study based on the laboratory test results that did not meet inclusion criteria, as defined in Section 9.3.1, had any individual laboratory parameter retested once within the 4-week (+2 weeks) Screening period at the discretion of the investigator. Retesting performed outside of the 4-week (+2 weeks) Screening period was considered rescreening (see Section 9.1.2.1.2).

9.1.2.1.2. Rescreening

Rescreening was permitted for patients who consented to participate in the study but did not initially meet all the requirements as outlined in the inclusion and exclusion criteria (Section 9.3) for reasons potentially reversible within a reasonable timeframe. In such case, agreement with the medical monitor was obtained before conducting additional Screening visits and/or repeated Screening assessments to establish eligibility.

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

When rescreening occurred, the individual was required to reconsent and was assigned a new identification number.

9.1.2.2. Screen Failures

Screen failures were defined as patients who consented to participate in the clinical study but did not meet one or more criterion required for participation and were not subsequently entered in the study (see Section 9.1.2.1.1 for retesting conditions). A minimal set of screen failure information (demographics and reason for screen failure) was required to ensure transparent reporting of screen

failure patients, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities.

9.1.3. Double-blind Treatment Period (24 weeks): Part A

A total of 57 patients who met all inclusion criteria and none of the exclusion criteria were planned to be randomized in a 2:1 ratio to receive either pegcetacoplan or placebo twice weekly for 24 weeks.

All standard-of-care medications could be continued, except for protocol-defined prohibited medications (see Section 9.4.7.1.2).

During this study period, patients received a blood transfusion if their Hb level was <7.0 g/dL. Transfusions were considered, at the investigator's discretion, in symptomatic patients with Hb levels ≥7.0 and <9.0 g/dL.

9.1.4. Open-label Treatment Period (24 weeks): Part B

All patients who completed the 24-week double-blind treatment period were eligible to enter the open-label treatment period, during which they received pegcetacoplan 1080 mg twice weekly for up to 24 weeks (Week 48).

9.1.5. Open-label Maintenance Period (up to additional maximum 48 weeks or until the product was commercially available): Part C

After completion of the open-label treatment period, patients who benefited from therapy without significant side effects were planned to continue receiving pegcetacoplan 1080 mg SC twice weekly for a maximum of 48 additional weeks or until the product was commercially available, whichever occurred first. When the commercial product was not available at the end of Part C, patients were to be managed outside of the current study on a case-by-case basis, in accordance with applicable laws and regulations.

9.1.6. Follow-up Period (8 weeks)

After completion of the open-label maintenance period or if patients discontinued investigational medicinal product (IMP) treatment early, an end of treatment (EOT) or early termination (ET) visit was performed, followed by an end of study (EOS) visit 8 weeks later. A schematic study design is presented in Figure 9-1.

9.1.7. Unscheduled Visits

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

9.2. Discussion of Study Design

In this double-blind, randomized, Phase 3 study, patients were randomized in a ratio of 2:1 to receive pegcetacoplan or placebo. The study enrolled patients affected by CAD who had a Hb level of ≤9 g/dL. There were no approved therapies for patients with CAD in need of treatment at the time of this study; therefore, the choice of placebo as comparator was fully justified.

The primary objective of the study was to demonstrate a significant effect of pegcetacoplan on Hb levels that was durable and effective in reducing the transfusion requirement. The treatment duration was 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 ongoing in the study, and 48 additional weeks to allow treatment continuity until the product was commercially available.

9.3. Selection of Study Population

Patients who met **all** the following inclusion criteria and **none** of the exclusion criteria were enrolled in the study.

9.3.1. Inclusion Criteria

1. Age 18 years or older
2. Diagnosis of primary CAD on the basis of the presence of **all** of the following criteria at Screening:
   a. Signs of hemolysis with abnormal values for at least 2 of the following hemolytic markers:
      i. Reduced haptoglobin level (<lower limit of normal [LLN])
      ii. Elevated LDH level (>upper limit of normal [ULN])
      iii. Elevated indirect bilirubin level (>ULN; >3 × ULN for patients with Gilbert-Meulengracht syndrome)
      iv. Increased absolute reticulocyte count (above the ULN).
   b. Monospecific direct antiglobulin test strongly positive for C3d.
   c. Cold agglutinin titer ≥64 at 4°C.
3. Hemoglobin level ≤9 g/dL at Screening.
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 had not received a bone marrow biopsy within 1 year of their Screening visit or for whom bone marrow biopsy reports were incomplete or unavailable were required to receive a bone marrow biopsy to determine eligibility.
6. Body weight ≤100 kg.
7. Either had vaccination against *Streptococcus pneumoniae* (*S. pneumoniae*), *Neisseria meningitidis* (*N. meningitidis*; Types A, C, W, Y, and B), and *Haemophilus influenzae* (*H. 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 IMP 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 IMP 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. This was not applicable for Japan as the *N. meningitidis* vaccine was not approved in Japan.

b. *S. pneumoniae*: PCV13 and/or PPSV23 as per Advisory Committee on Immunization Practices (ACIP) guidelines for adults or children with immunocompromising conditions.

c. *H. influenzae* Type B: 1 dose at least 2 weeks prior to start of the IMP.

Vaccination was mandatory unless documented evidence existed that patients were non-responders to vaccination. Vaccinations were to be administered following the ACIP recommendations for adults or children with complement deficiencies and/or immunocompromising conditions.

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

Notes:

a. Postmenopausal was defined as having had 12 consecutive months with no menses without an alternative medical cause.

b. Intravaginal, transdermal, injectable or implantable forms of hormonal contraception methods were prohibited in Japan.

9. Men had to 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.

9.3.2. Exclusion Criteria

1. Had 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 15 weeks) and are not able or willing to refrain from using them during the study. Patients previously treated with >1 dose of sutimlimab were excluded if they did not experience a documented increase in Hb ≥1.0 g/dL during sutimlimab treatment.

2. Treatment with belimumab, rituximab or other anti-CD20 antibody (such as obinutuzumab or ocrelizumab), or with bendamustine, fludarabine, other cytotoxic drugs, or Bruton tyrosine kinase inhibitors such as ibrutinib, acalabrutinib and zanubrutinib, alone or in combination with rituximab within 16 weeks prior to randomization.

Note: The exclusion criteria #1 and #2 detailed above, were updated in the protocol version 5 (dated 13 March 2023). Hence, few patients were recruited before protocol version 5 was

effective for whom the updated criteria of exclusion for #1 (previous wording: patients previously treated with >1 dose of sutimlimab will be excluded if the patients have not experienced a documented increase in Hb ≥1.0 g/dL during sutimlimab treatment; the cut-off period for a patient to be excluded from the study due to sutimlimab treatment was 4 weeks) and #2 (previous wording: treatment with belimumab or other anti-CD20 antibody [such as obinutuzumab or ocrelizumab] or Bruton tyrosine kinase inhibitors such as acalabrutinib or zanubrutinib, alone or in combination with rituximab within 16 weeks prior to randomization) were not applicable.

3. Use of prohibited medications as described in Section 9.4.7.1.2. Refer to Section 9.4.7.1.1 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 (antinuclear antibodies of long-standing duration without associated clinical symptoms will be adjudicated on a case-by-case basis by the investigator after discussion with the medical monitor).
5. History of an aggressive lymphoma or presence of a lymphoma requiring therapy.
6. Had received an organ transplant.
7. Cold agglutinin syndrome secondary to *Mycoplasma pneumoniae*, *Epstein-Barr virus* or other specific causative infection. In patients with long history of CAD, positive IgM titer and IgG titer without associated clinical symptoms were to be adjudicated on a case-by-case basis by the investigator after discussion with the medical monitor.
8. Human immunodeficiency virus (HIV) or hepatitis C virus detectable by polymerase chain reaction at Screening or documented in the patient's medical record.
9. Chronic hepatitis B virus carriers with viral loads >1000 IU/mL (>5000 copies/mL) at Screening or documented in the patient's medical record. Eligible patients who were chronic inactive carriers (≤1000 IU/mL) had to 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 was 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 × ULN, or direct bilirubin levels >2 × ULN. For any patient with increased direct bilirubin, the investigator was to exercise medical judgement to ensure that the increased direct bilirubin value was due to hemolysis and discuss inclusion with the medical monitor. If the direct bilirubin was higher than the indirect bilirubin, in addition a thorough search for exclusion of underlying liver or cholestatic disease, including but not necessarily limited to abdominal ultrasound, was warranted to exclude liver and/or cholestatic disorders.
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, was 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 could cause reasonable suspicion of a disease or condition that could jeopardize the patient's wellbeing, that could increase the risk associated with study participation, that may affect the interpretation of the results, or that could make the patient unsuitable for this study.
21. Protected adults (guardianship, trusteeship) who were unable to express their consent and persons under court protection.
22. Any infection (including COVID-19) requiring hospitalization or treatment with intravenous anti-infectives not resolved within 2 weeks prior to the first dose of the IMP.

9.3.3. Withdrawal of Patients from Treatment or Study

9.3.3.1. Withdrawal from Treatment

All patients had the right to withdraw at any point during study participation without prejudice. When a patient was withdrawn from the treatment, the medical monitor was to be immediately notified and the date of last IMP dose and the date and reason for treatment withdrawal were to be clearly described in the relevant sections of the electronic case report form (eCRF). Whenever a patient was removed from the treatment because of a treatment-emergent adverse event (TEAE), the reason for treatment withdrawal was to be stated as 'TEAE' irrespective of whether it was the investigator's or the patient's decision.

Pegcetacoplan was to be discontinued if any of the following laboratory abnormalities and/or TEAEs were observed that were assessed as causally related to the IMP (i.e., no alternative explanation was identified) by the investigator.

- Any Grade ≥3 non-hematological laboratory abnormality (other than Grade 3 hypoglycemia; Grade 3 aspartate aminotransferase [AST], gamma glutamyl transferase [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 non-hematological toxicity (other than Grade 3 nausea, vomiting, or diarrhea ≤72 h in duration with adequate prophylactic and supportive care)

- A severe hypersensitivity reaction (including anaphylaxis): The IMP was to be immediately permanently discontinued and appropriate treatment instituted.

Patients were to be permanently discontinued from the study treatment if they:

- Used prohibited medications (Section 9.4.7.1.2) during the study
- Were pregnant

In these cases, patients could continue to participate in the study without taking study treatment. Patients who stopped study treatment prior to the exit visit had to undergo all follow-up visits and procedures through study completion, unless they were unwilling or unable or withdrew consent.

9.3.3.2. Withdrawal from Study

A patient could withdraw from the study at any time at their own request or at the request of their legally authorized representative or could be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This was expected to be uncommon. Whenever possible and irrespective of the reason for withdrawal, the patient was examined as soon as possible. Relevant samples were obtained, and all relevant assessments were completed. The eCRF was completed as far as possible with the date and reason for the study withdrawal clearly described in it. Once a patient left the study, they could not re-enter the study.

9.3.3.3. Lost to Follow-up

A minimum of 3 documented attempts had to 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 included 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.

If the patient continued to be unreachable, they were to be considered withdrawn from the study.

9.3.3.4. Replacement of Withdrawn Patients

Withdrawn patients were not replaced.

9.3.4. Stopping or Suspending the Study

The study enrollment could be suspended when:

- Two patients from 2 different investigational sites experienced a Grade 4 TEAE assessed as related to the IMP by the investigator.
- One patient experienced a Grade 5 TEAE assessed as related to the IMP by the investigator.

The sponsor was to thoroughly evaluate the reported adverse reactions and resume the study only if an alternative explanation of the reported events was identified. In case the decision to stop the study was made, the sponsor was to communicate the appropriate action for ongoing patients who were on treatment with the active drug based on the risk-benefit assessment. The sponsor or designee was to 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 was to inform the IRB and IEC.

Sponsor reserved the right to close the study site or terminate the study at any time for any reason at their sole discretion.

Unjustifiable risk and/or toxicity or substantial changes in risk-benefit considerations, which could raise medical and/or ethical reasons affecting the continued performance of the study, could cause premature termination of the clinical study or one of the study parts.

The following criteria could cause premature termination of a study site:

- Favorable opinion withdrawn by the IRB and IEC or local health authorities.
- Failure of the investigator to comply with the protocol, the requirements of the IRB and IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Withdrawal of the license to manufacture and/or of the permission to import.

If the study was prematurely terminated or suspended, the sponsor was to promptly inform the investigators, the IRBs and IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator was to promptly inform the patient and assure them of the appropriate therapy and/or follow-up.

9.4. Treatments

9.4.1. Treatments Administered

9.4.1.1. Investigational Medicinal Products

The pegcetacoplan treatment group received a dosage of 1080 mg twice weekly via SC infusion (20 mL) while the placebo group received placebo SC infusion twice weekly during the double-blind treatment period (24 weeks).

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

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

9.4.1.2. Vaccination and Preventive Antibiotics

9.4.1.2.1. Vaccination

To receive treatment with IMP, patients were to be vaccinated as per ACIP recommendations for adults or children with complement deficiencies and/or immunocompromising conditions.

Patients previously vaccinated had 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 vaccine (see Section 9.3.1, Inclusion Criterion #7).

Patients who were not previously vaccinated had to receive vaccines during Screening as stated below:

- First dose of vaccine against *N. meningitidis* Types A, C, W, and Y at least 2 weeks prior to start of the IMP 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 the IMP 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. This was not applicable for Japan as the *N. meningitidis* vaccine is not approved in Japan.
- *S. pneumoniae*: PCV13 and/or PPSV23 as per ACIP guidelines for adults or children with immunocompromising conditions.
- *H. influenzae* Type B: One dose at least 2 weeks prior to start of the IMP.

Vaccination was mandatory, unless documented evidence existed that patients were non-responders to vaccination. Documented evidence that a patient was a non-responder to vaccination had to be provided via serological result (after second dose or booster where applicable). The investigator would discuss with the sponsor regarding individual patient circumstances.

In Japan, adverse reactions such as pain, redness, and swelling at the injection site were more commonly reported if the polyvalent pneumococcal vaccine was administered within five years of a previous dose. The necessity and timing of re-vaccination were carefully considered in this study (see Table 9-2).

Vaccines were sourced locally by the study sites and reimbursed by the sponsor or sourced by the sponsor when local sourcing was not feasible.

9.4.1.2.2. Preventive Antibiotics

To receive treatment with IMP, patients who were documented as non-responders to vaccination or could not be vaccinated prior to IMP initiation received prophylactic antibiotics according to local standard practices.

9.4.2. Identity of Investigational Products

Pegcetacoplan was provided as a sterile, clear, colorless to slightly yellowish aqueous solution of pegcetacoplan at 54 mg/mL (1080 mg/20 mL) in 10 mM acetate buffer, potential of hydrogen (pH) 5.0, containing 4.1% sorbitol, provided in single use stoppered glass vials.

Placebo was 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 IMPs were to be reported to the study medical monitor and to complaints@sobi.com.

9.4.2.1. Packaging

The IMP was supplied in 20-cc glass vials.

All IMPs were packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

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

9.4.2.2. Storage

The sponsor supplied syringes, vial adapters, infusion sets, ambulatory syringe infusion pumps, and any other supplies needed for the safe home IMP administration as required.

All IMPs were stored in a refrigerator between 2 to 8°C, protected from light, both at home and in the clinic. Temperature monitoring was required at the investigator site (or documented storage location) to ensure that the IMP was maintained within an established temperature range.

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

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

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

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

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

When the patient received the IMP from the site, it was 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) was maintained. Temperature monitoring was not required during transport or at the patient's residence. It was 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.

9.4.2.3. Accountability

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

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

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

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

9.4.3. Avoidance of Bias

9.4.3.1. Method of Assigning Patients to Treatment Groups

Randomization occurred through the Interactive Response Technology (IRT) system.

Eligible patients were randomly assigned through the IRT system to either pegcetacoplan or placebo in a 2:1 ratio. The randomization was stratified according to number of transfusions during the 6-month period prior to randomization (≥1; 0). Every effort was 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 were provided to each study site. IMP dosing was initiated at the site after randomization. At each visit when IMP was administered and dispensed, the study staff contacted the IRT to obtain appropriate kit numbers.

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

9.4.3.2. Blinding and Unblinding

9.4.3.2.1. IMP Blinding

Pegcetacoplan and placebo products were of identical appearance.

The IMP blind was 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 remained blinded to treatment allocations until all patients completed Week 24 assessments and the database had been locked in for the analysis at Week 24. The IMP blinding was maintained through Week 24, except for one patient who required emergency unblinding.

Certain laboratory data could potentially hint at the possibility that the patient was on active treatment; however, these also represent safety parameters and, therefore, investigators were not blinded to hematology and safety laboratory results. Both sponsor and investigators were blinded through the Week 24 primary endpoint analysis for the following laboratory parameters: anti-pegcetacoplan peptide and anti-polyethylene glycol (PEG) antibodies, complement profile, pegcetacoplan concentrations, and pharmacokinetic (PK) parameters.

After Week 24, all patients received open-label pegcetacoplan.

9.4.3.2.2. IMP Unblinding

- Emergency unblinding

Unblinding, i.e., breaking the code for an individual patient during the study, was restricted to emergency situations and was only used under circumstances where knowledge of the treatment

assignment was necessary for the proper handling of the patient. Emergency unblinding was to be performed through IRT system.

The investigator had to 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 was necessary for clinical management. Once a patient's treatment assignment had been unblinded, the study medical monitor and study coordinator were notified within 24 h 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) were clearly recorded in the patient's study file and in the electronic data capture (EDC) system as part of relevant standard operating procedures. In addition, the investigator had to consider whether the clinical event prompting unblinding was to be considered a TEAE or treatment-emergent serious adverse event (TESAE) according to the criteria for TEAEs or TESAEs (see Section 9.5.2.1), and if so, such event was to be reported accordingly.

- Unblinding for suspected unexpected serious adverse reactions

When a suspected unexpected serious adverse reactions (SUSAR) occurred in a patient participating in the study, Sobi Global Pharmacovigilance & Patient Safety could request the unblinding of the treatment assignment. The randomization code was not required to be communicated to the site staff, or to the Sobi study team; unblinded SUSAR information was to be provided to respective Health Authorities.

9.4.4. Dose Selection and Timing for Each Patient

A twice-weekly dose of 1080 mg was selected as the dosing regimen on the basis of PK modeling, which predicted 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 SC administration was confirmed in a study of healthy subjects (e.g., Study 101; refer to the pegcetacoplan investigator's brochure [IB], Edition 11) (Pegcetacoplan-APL-2-IB 2023).

Population PK modeling based on pooled data from 10 clinical studies, including data up to Week 6 from Study APL2-302, confirmed that the pegcetacoplan exposure achieved at a dosage of 1080 mg SC twice weekly was intermediate to those predicted for dosages of 270 mg and 360 mg SC once daily (refer to pegcetacoplan IB).

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

Patients could self-administer or get caregiver's (a member of the patient's household, a family member) help to administer SC IMP, after receiving appropriate training by research personnel. IMP was dosed at the clinical site on Day 1. On dosing days that coincided with clinic visits, doses were administered at the clinic visit. Self-administration or caregiver administration conducted at

the clinic was supervised to ensure that the patient or caregiver continued to remain compliant with the administration guidelines.

Note: The administration of IMP by caregivers was not allowed in Japan according to Medical Practitioners' Act. Only qualified person such as physician or by nurse, or self-administration by patient only in the case of self-injection at home.

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

Dosing diaries were completed for each dose administered at the clinic or at home. Patients were not to 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 was abdomen. If administration into the abdomen was not feasible, alternative appropriate sites were acceptable. The typical SC infusion time for pegcetacoplan was approximately 30 min when 2 sites were used, or approximately 60 min when 1 site was used.

Missed doses were 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 had already been administered.

NOTE: If the patient or caregiver required further training, the self-administration qualification period was to be extended as needed. Caregiver training was not applicable for Japan.

9.4.5. Dose Modification

Any dose modification (treatment interruption/discontinuation) required to manage TEAEs were to be discussed with the study medical monitor.

9.4.6. Treatment Compliance

Dosing diaries were used for pegcetacoplan and were completed for each dose administered at the study site or outside regular clinic visits. Patients were not to deviate from their dosing schedule.

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

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

The pharmacist/designee recorded details on the drug accountability form. Refer to the Pharmacy Manual for further details.

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

9.4.7. Prior and Concomitant Therapy

Details of the patient's current and prior medications and procedures were obtained. All medications administered and procedures performed within 12 weeks before ICF signature were recorded as prior medications and procedures. Medications administered and procedures performed from the time of informed consent through the EOS visit were recorded as concomitant medications and procedures.

9.4.7.1. Prior and Concomitant Medications

Prior medications refer to the medications administered within 12 weeks before the time of informed consent. 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. The medications started before informed consent but continuing after were considered as both prior and concomitant medications. Prior and concomitant medication information was recorded on the appropriate eCRF page and the data were presented by treatment group and overall. 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 were given at the discretion of the investigator. It was the responsibility of the investigator to ensure that the details regarding all medications were recorded in full in the patient's eCRF. All prior and concomitant medications were coded using the latest version of World Health Organization drug dictionary (WHO Drug Global Version September 2024). In any given category (e.g., drug category), a patient was counted only once.

9.4.7.1.1. Permitted Therapy

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

- Stable dosage for at least 4 weeks prior to randomization:
  - Erythropoietin.
  - Corticosteroids. If a patient, per the investigator's opinion, required corticosteroids initiation during the study for reasons other than CAD, a discussion with the study medical monitor was required before starting treatment. Topical, inhalation, or intraarticular use of corticosteroids was permitted.
  - Vitamin K antagonists (e.g., warfarin) with a stable international normalized ratio (INR).
  - Direct oral anticoagulants.
  - Iron supplements, vitamin B12 or folic acid. If patients had previously received and tolerated iron chelation, this could 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.

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

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

9.4.7.1.2. Prohibited Medications

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

- Rituximab or any other anti-CD20 antibody (alone or in combination).
- Any other complement inhibitor (e.g., eculizumab, ravulizumab, or sutimlimab).
- Bortezomib.
- Any other investigational drug.
- Plasma exchange.

Phlebotomy/venesection for iron overload was also prohibited during Part A of the study.

These medications were prohibited because they could interfere with the evaluation of the study endpoints. The use of prohibited medications during the study would require the patient to be permanently discontinued from the study treatment.

9.5. Efficacy and Safety Evaluation

The schedule of activities is provided in Protocol Table 1 and Table 2 (Appendix 16.1.1).

9.5.1. Efficacy Assessments

All Baseline assessments were performed on Day 1 before dosing. If it was convenient for the patient and/or the site due to logistic reasons, Baseline assessments were performed the day before first IMP dosing.

9.5.1.1. Hemoglobin level and other laboratory efficacy assessments

The primary and other secondary efficacy assessments (i.e., Hb, LDH, haptoglobin, indirect bilirubin, ARC, and D-dimer) were based on laboratory parameters and are described in Section 9.5.2.2.

For the primary efficacy assessment, response was 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 LLN and ULN), maintenance of this effect from Week 16 to Week 24, and the absence of PRBC transfusions between Weeks 5 and 24.

9.5.1.2. Transfusions

All the RBC transfusions performed during the study period from Screening until EOS were recorded.

9.5.1.3. Health-related quality of life

The functional assessment of cancer therapy-anemia/fatigue score (FACT-An) is a useful measure of quality of life in cancer patients that adds focus to the widespread clinical problems of anemia (Cella 1997). 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.

The 12-item short form survey (SF-12) is a self-reported outcome measure assessing the impact of health on an individual's everyday life (Ware 1996). 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.

The 5-level EuroQol 5-dimension (EQ-5D-5L) is a standardized instrument for measuring generic health status (Herdman 2011). 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).

9.5.1.4. 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) are appropriate measures to assess such efficacy objectives.

9.5.2. Safety Assessments

Patients were observed for general appearance, presence of illness or injury, or signs indicative of current illness at all the time points in Protocol Table 1 and Table 2 (Appendix 16.1.1). Patients were instructed to volunteer any information regarding TEAEs on or after the first dose of IMP, or the patients were queried regarding any TEAEs they could have been experiencing (e.g., "How have you been feeling since your last visit?"). Patients were also asked if they had been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Any responses or findings were documented.

9.5.2.1. Adverse Event Definitions

9.5.2.1.1. Adverse Events

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

AEs included the following:

- Abnormal test findings (described in the Section 9.5.2.1.2)
- 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 pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the study even though it may have been present prior to the start of the study.

- Continuous persistent disease or symptoms that was present at study start and worsened following the start of the study.

9.5.2.1.2. Abnormal test findings

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

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

9.5.2.1.3. Pre-existing conditions

A pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the pre-treatment medical history/physical examination form) was not reported as an AE unless the condition worsened, or episodes increased in frequency during the AE reporting period.

9.5.2.1.4. AE diagnosis versus signs/symptoms

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

9.5.2.1.5. Procedures

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

9.5.2.1.6. Treatment-emergent Adverse Events

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

9.5.2.1.7. Serious Adverse Events

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

- Resulted in death.
- Was life threatening (i.e., at immediate risk of death).
- Required in-patient hospitalization or prolongation of existing hospitalization.

- Resulted in persistent or significant disability/incapacity.
- Was a congenital anomaly/birth defect (i.e., in an offspring to the study patient).
- Was a medically important AE.

Medically important AEs are events that may not result in death, be life threatening, or require hospitalization, but considered serious when, based upon appropriate medical judgment, may jeopardize the patient 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.

SAEs also included any other event that the investigator or company judged to be serious. Any suspected transmission of an infectious agent via IMP was also to be considered serious.

All SAEs were to be reported by the investigator to the Sobi Global pharmacovigilance and Patient Safety within 24 h of the investigator's first knowledge of the event.

The detailed definition of SAEs in this study (and how they were elicited, reported, and followed) are standard for clinical trials and are described in Protocol Section 6.5.4.1.1 through Section 6.5.4.1.6 (Appendix 16.1.1).

9.5.2.1.8. Suspected Unexpected Serious Adverse Reaction

A SUSAR is an untoward and unintended response to an IMP 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. Causality was also reported for auxiliary medicinal product in Europe and to the infusion pump in Japan.

9.5.2.2. Laboratory Tests

Laboratory assessment samples detailed in Table 9-1.

It was ensured that the Baseline hematology sample was available before the first IMP dosing. If needed, the sample could be obtained the day before first IMP dosing.

Table 9-1. Laboratory Parameters

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	Estimated glomerular filtration rate (using CKD-EPI formula) GGT Glucose Haptoglobin LDH Phosphorous Potassium Sodium

Table 9-1. Laboratory Parameters

	Creatinine Creatine kinase	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 Serum pegcetacoplan concentration (PK)

Source: Protocol Table 4

a. The use of silica reagents in coagulation panels was avoided in all patients.

Abbreviations: Ab=antibody; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; ARC=absolute reticulocyte count; 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 glutamyl transferase; Hb=hemoglobin; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IFNγ=interferon-gamma; IgA=immunoglobulin A; IgG=immunoglobulin G; IgM=immunoglobulin M; IL-6=interleukin-6; IL-10=interleukin-10; IL-1β=interleukin-1 beta; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PEG=polyethylene glycol; PK=pharmacokinetics; RBC=red blood cells; RNA=ribonucleic acid; TNFα=tumor necrosis factor alpha; WBC=white blood cells.

If the Screening period was extended beyond 4 weeks, in addition to the regular Baseline serum chemistry to be analyzed in the central laboratory, a local safety serum chemistry sample including at least blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin (total, direct and indirect), chloride, sodium, potassium, phosphorus, calcium, and glucose was obtained up to 7 days before dosing and ensured to be available to the investigator before first IMP dosing. This sample was only obtained to ensure continued safety of dosing, and

only the results of the central laboratory evaluation were considered in the general study evaluation.

All laboratory reports were to be reviewed, signed, and dated by the investigator. A legible copy of all reports was 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 was considered as an AE (see Section 9.5.2.1.1 for details). Clinically significant abnormal values that occurred during the study were followed up until repeat test results returned to normal, stabilize, or were no longer clinically significant.

If a patient had been tested for COVID-19, the results, if available, were documented in the eCRF.

9.5.2.2.1. Pregnancy tests

For WOCBP, a serum pregnancy test was performed at Screening, and urine pregnancy tests were performed on Day 1. The use of the local laboratory was allowed for the Baseline pregnancy tests to ensure that results were available prior to dosing on Day 1. A urine pregnancy test was also performed on Weeks 1, 2, and 4, and then every 4 weeks through the end of the study, including the Follow-up visit, by using a home test if there was no clinic visit. Patients with positive results were excluded or discontinued from the study. Urine pregnancy test was to be completed prior to dosing on days where dosing coincided with clinic visits.

9.5.2.3. Immunogenicity Assessments

Patients had anti-drug antibody (ADA) samples collected as outlined in the schedule of assessments (Protocol Table 1 and Table 2 [Appendix 16.1.1]). 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 antibody formation while minimizing pegcetacoplan level in the sample. Patients who were confirmed ADA positive in the last dosed sample were followed up with ADA samples being collected every 6 months until the antibody levels returned to Baseline.

ADA samples were analyzed for the presence of anti-pegcetacoplan peptide and anti-PEG antibodies. The common three-tiered approach was employed for both anti-pegcetacoplan peptide and anti-PEG. The assay detecting anti-pegcetacoplan peptide ADA (specific for antibodies that bind the peptide domain) was a validated bead-based MSD (Meso Scale Discovery) Solid Phase Extraction with Acid Dissociation assay using labeled pegcetacoplan peptide for capture. The assay detecting anti-PEG ADA was a validated direct binding ELISA (enzyme-linked immunosorbent assay). Specific antibody titers were determined in all samples that were confirmed positive for anti-pegcetacoplan peptide or anti-PEG antibody. Any samples that were confirmed positive for anti-pegcetacoplan peptide antibody were further characterized with a neutralizing antibody (NAb) assay. NAb was determined using a validated competitive MSD assay, where NAbs prevent the binding of labeled complement C3 (used as detection) to pegcetacoplan causing a reduction in signal. More details regarding ADA and NAb analyses are described in dedicated bioanalytical reports (Appendix 16.1.13).

9.5.2.4. Vital Signs

Vital signs (body temperature, respiratory rate, heart rate, systolic and diastolic blood pressure) were evaluated at the visits indicated in the protocol schedule of assessments tables. All vital signs were measured after the patient had been resting in a sitting position for at least 5 min, except when supine or semi-reclined because of study procedures and/or AEs or if deemed necessary by the investigator. Blood pressure measurements were taken in the same arm for the duration of the study.

When the IMP was administered at the study site, vital signs were measured within 2 h before dosing and venipuncture (and ECG, if applicable) and at 30 min (±5 min) post-dose.

Vital signs measurements were to be repeated, when clinically significant or when machine/equipment errors occurred. Out-of-range blood pressure, respiratory rate, or heart rate measurements were to be repeated at the investigator's discretion. Any confirmed, clinically significant vital signs measurements were to be reported as AEs (see Section 9.5.2.1.1 for details).

9.5.2.5. Weight and Height

Body weight and height (both assessed without shoes on) were recorded at Screening. Weight was also recorded at each physical examination.

9.5.2.6. Physical Examination

Full physical examinations performed by the investigator/designee included 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 included general appearance, heart, lungs, abdomen and extremities, and were to be performed at all visits where a full physical examination was not performed.

See the schedule of assessments (Protocol Table 1 and Table 2 [Appendix 16.1.1]) for the details regarding which type of physical examination was performed at each visit.

If any abnormalities were reported at Screening, they were to be recorded as medical history. New or worsening of abnormalities after first IMP dosing were reported as AEs (see Section 9.5.2.1.1 for details).

9.5.2.7. Electrocardiograms

Single 12-lead ECGs were measured prior to dosing at the time points outlined in the protocol schedule of assessments. The ECG was to be taken after the patient had been resting in the supine position for 5 min in a quiet environment and prior to any blood sampling procedures, unless specified at time points after timed blood sampling procedures.

The ECGs were 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 IMP was to be documented in the medical history section of the eCRF. Any significant ECG finding with an onset time after IMP initiation and that were not present at Screening, or worsened during the study, was to be reported as an AE (see Section 9.5.2.1.1 for details).

9.5.2.8. Infusion-site Reactions/Pump-safety Assessments

When the scheduled dosing day coincided with a clinical visit, the patient or their caregiver had to perform their infusion at the clinic in presence of the investigator or other trained and qualified site staff. Patients or their caregivers (except in Japan) were trained to administer IMP at home.

On the days of clinic visits, an assessment of the pegcetacoplan infusion site was made as a part of the AE assessment. If pegcetacoplan was administered at the visit, the site staff observed the dosing and assessed pump use safety. The infusion site was to be checked again within 30 min after IMP administration. The infusion-site assessments were performed by an appropriately trained staff, as delegated by the investigator. The infusion site and surrounding area were inspected for redness, swelling, induration and bruising. The patients were 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 were recorded on the source documents and eCRFs.

Patients were instructed to notify the investigator or other study personnel if an infusion-site reaction occurred after self-administration of pegcetacoplan. All clinically relevant AEs, as determined by the investigator, from infusion site or related to pump use were recorded as AEs (see Section 9.5.2.1.1 for details).

9.5.2.9. Appropriateness of Safety Measurements

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

9.5.3. Pharmacokinetic Assessments

Blood samples for the PK assessment of pegcetacoplan were collected via direct venipuncture at the time points outlined in the protocol schedule of assessments tables. PK samples were taken within 15 min before the administration of the IMP and strictly before the start of dosing.

Instructions for collection, handling, processing, storage, and shipping of samples were provided in a separate sample handling manual prior to study initiation. Serum sample analysis was performed using validated method consisting of a protein precipitation extraction followed by LC-MS/MS (Liquid Chromatography coupled to tandem Mass Spectrometry) instrumental analysis. All details regarding serum sample PK analysis are described in a dedicated bioanalytical report (Appendix 16.1.14).

9.5.4. Pharmacodynamic Assessments

Serum samples for pharmacodynamic (PD) assessment of complement activation through functional assays for classical and alternative complement pathways as well as C3 levels were collected on study days designated in the protocol schedule of assessments tables. Activation of the classical pathway was measured in a validated assay (CH50 assay) via complement-mediated hemolysis of IgG-coated sheep RBCs. Activation of the alternative pathway was measured in a validated assay (AH50 assay) via complement-mediated hemolysis of rabbit RBCs. C3 levels were measured using a validated nephelometry method. C3 deposition on RBCs was analyzed in whole blood using a validated flow cytometry method.

Measurement of tumor necrosis factor-alpha (TNFα), interleukin-6 (IL-6), interleukin-10 (IL-10), interferon-gamma (IFNγ), and interleukin-1-beta (IL-1β) was carried out on serum samples using

a validated MSD multiplexed panel. All details regarding serum sample PD analyses are described in dedicated bioanalytical reports (Appendix 16.1.15).

9.5.5. Other Measurements

9.5.5.1. MYD88 Mutation Testing

Bone marrow biopsy was to be performed at Screening only when 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 could be performed locally on aspirate during Screening. If the MYD88 genetic mutation testing was performed already according to the local institutional standard of care, the result was to be collected at Screening.

9.6. Data Quality Assurance

Information about study risks identified, evaluated, reviewed, and reported as well as risk mitigation is provided in the Risk Management Plan that is available in the Trial Master File.

9.6.1. Study Monitoring

Before an investigational site began enrolling patients into the trial, a representative of the sponsor visited the investigational site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the sponsor or its representatives.

During the study, a Clinical Research Associate (CRA) from the sponsor or representative had regular contact with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remained acceptable.
- Confirm that the investigational team was adhering to the protocol, that data were being accurately recorded in the eCRFs, and that investigational product accountability checks were being performed.
- Perform source data verification. This included a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study.
- Record and report any protocol deviations to the sponsor.
- Confirm AEs and SAEs had been properly documented on the eCRFs and confirmed any SAEs had been forwarded to the sponsor and that those SAEs that met criteria for reporting had been forwarded to the IRB and IEC.

The CRA was available between visits if the investigator(s) or other staff needed information or advice.

Additionally, medical monitors reviewed the clinically relevant data points to provide independent medical and safety oversight to protect the safety of the study patients and the integrity of data.

9.6.2. Audits and Inspections

Authorized representatives of the sponsor or designee, a Regulatory Authority, or IRB and IEC could visit the site to perform audits or inspections, including source data verification. The purpose of a sponsor audit or inspection was to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, International Council for Harmonization (ICH) GCP guidelines, and any applicable regulatory requirements. The investigator was to contact the sponsor immediately if contacted by a Regulatory Agency about an inspection.

The following audits were performed:

Site Number/Investigator Name	Type of Audit	Dates of Audit
4401 /UK	Sponsor audit	20 July 2023 and 21 July 2023
4701 /Norway	Sponsor audit	04 December 2023 and 05 December 2023
3901 /Italy	Sponsor audit	11 January 2024 and 12 January 2024

Copies of the audit certificates are provided in Appendix 16.1.8.

9.6.3. Quality Control and Quality Assurance

9.6.3.1. Data Processing

The study was run as an EDC trial, i.e., all relevant data were entered by the site directly into the clinical database. The database and application were set up and managed by Allucent.

9.6.3.2. Electronic Case Report Forms

Electronic case report forms were used for data collection. The Zelta EDC system was designed to capture all required information in compliance with GCP standards. Following training, study staff were given access to the eCRF and were provided with eCRF guidelines. Access to the database was restricted to staff participating in the study and the extent of access was dependent on the participants' user role in the study.

The study participants were identified in the database by patient numbers. The investigator or delegate was to enter patient data into the eCRF within 2 working days (if possible). Data recorded in the eCRFs were accessible to the study staff throughout the study.

After data entry, systematic data validation was performed, and data entry discrepancies were presented electronically directly to the site staff. Queries for discrepant data could be generated automatically by the software upon entry and/or generated manually by the CRA or the Data Manager. All queries, whether generated by the system or by study staff, were in electronic format.

All sections of the eCRF were electronically approved by the investigator after the data were entered and all queries have been resolved. Changes to any eCRF page subsequent to the approval required a new approval signature.

All queries and changes/corrections to the data were documented in the eCRF.

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

Information for this section is in the statistical methods section of the protocol and in the final statistical analysis plan (SAP; Appendix 16.1.9). The SAP, which describes in detail the methods used for the primary and key secondary, other secondary, and safety endpoints, governed all statistical analyses.

9.7.1. General Considerations

- All analyses and summaries were produced using SAS® version 9.4.
- Categorical variables were summarized using the number of observations (n), frequency and percentage of patients.
- Continuous variables and ordered categorical data were summarized using the number of patients with evaluable data, mean, standard deviation (SD), geometric mean (where appropriate), median, first and third quartiles, minimum and maximum. For ordered categorical data and nominal data, absolute counts, and relative frequencies (in %) were calculated.
- All statistical hypothesis tests and confidence intervals (CIs) were 2-sided, using a type I error rate of 0.050.

9.7.2. Analysis Populations

A total of 6 analysis sets were to be defined:

- **Screened set**: The screened set included all patients who provided written informed consent. This set was used only for the purpose of describing patient disposition.
- **Safety set**: The safety set included all patients who received at least 1 dose of IMP. Patients were analyzed according to the treatment they received. This set was used for all safety analysis.
- **Intent-to-Treat (ITT) set**: The ITT set included all randomized patients. Patients were analyzed according to their assigned treatment, regardless of the treatment they actually received. The ITT set was used for all efficacy analyses.
- **Per-protocol (PPS) set**: The PP set included all patients in the ITT set who had not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. As part of the early termination adjustment to the analysis plan, it was decided that no analysis should be based on the PPS. Hence the PPS was never defined. Due to this reason, no exclusions from the analysis population were done due to Protocol Deviations.
- **PK set**: The PK set included all patients in the ITT set who received IMP and had at least 1 evaluable post dose PK measurement.
- **PD set**: The PD set included all patients in the ITT set who received IMP and had at least 1 evaluable post dose PD measurement.

9.7.3. Efficacy Analysis

9.7.3.1. Primary Efficacy Analysis

The primary efficacy endpoint was a responder analysis at Week 24, where response was defined as:

- An increase in Hb level 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 packed red blood cell (PRBC) transfusions (between Week 5 and Week 24).

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

Maintenance of effect was 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.

If response could not be evaluated (Hb at Week 16 and/or at Week 24 was missing), the patient was considered as a non-responder. If data at Week 20 were missing, the average of Week 16 and Week 24 was used to calculate maintenance of effect.

The absence of PRBC transfusions was assessed from Day 29 and until the end of the double-blind period (Week 24 or early withdrawal).

The primary efficacy analysis was conducted on the ITT set.

The estimand was a composite, considering patients having an intercurrent event (ICE) as non-responders. The ICEs of interest were:

- Withdrawal from treatment or lost to follow-up before the 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 responded were tabulated by treatment group and compared between treatment groups using an exact Cochran-Mantel-Haenszel (CMH) test stratified for the criterion used for stratification of randomization (≥1/0 transfusions during the 6-month period prior to randomization). The odds ratio of being a responder for the pegcetacoplan treatment group versus the placebo group and associated exact 95% CI and p-value were provided. The responder rate, difference between treatment groups, and 95% CI were also reported.

Subgroup analyses on the primary endpoint were conducted for:

- The strata with ≥1/0 transfusions during the 6 months prior to randomization. Fisher's exact test was used for this subgroup analysis
- The subgroups of patients previously treated with rituximab/rituximab-naïve patients

Baseline was taken as the last measurement prior to the first dose of IMP. All efficacy data were listed.

9.7.3.2. Secondary Efficacy Analysis

9.7.3.2.1. Key secondary efficacy endpoint analyses

The key secondary efficacy analyses were analyzed based on the ITT set.

To preserve the Type 1 error, a fixed-sequence testing strategy was used; hence, statistical significance of the first key secondary endpoint analysis was only concluded when statistical significance was achieved with the primary analysis of the primary endpoint. The ordering of the key secondary endpoints in this testing strategy was:

- 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 was applied to the primary and key secondary endpoints, no further multiplicity control was applied.

For all key secondary endpoints, subgroup analyses were presented for the following subgroups:

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

9.7.3.2.1.1. Change from Baseline to Week 24 in Hb level

The ICEs for the change from Baseline to Week 24 in Hb analysis, and their associated strategies to handle them were:

- Withdrawal from treatment or lost to follow-up before the end of the double-blind period (all measurements after withdrawal or lost to follow up were set to missing)
- Use of prohibited medications (all measurements after prohibited medication start date were set to missing)
- Transfusion from Week 5 to Week 24 (all measurements after transfusion were set to missing)

The change from Baseline to Week 24 in Hb was 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 to calculate the degrees of freedom.

This MMRM analysis implicitly imputed the data that was set to missing after an ICE resulting in a hypothetical strategy for handling the ICEs. The difference between treatment groups was estimated for each visit, along with its 95% CI and p-value.

9.7.3.2.1.2. Transfusion avoidance (Yes/No) from Week 5 to Week 24

Transfusion avoidance (Yes/No) from Week 5 to Week 24 (Day 29 until end of double-blind period, which was Week 24 or early withdrawal) were tabulated by treatment group and compared between treatment groups using an exact CMH test stratified for the criterion used for randomization stratification (≥1/0 transfusions during the 6-month period prior to randomization). 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 was provided.

The composite strategy was used as the estimand, wherein patients meeting any of the ICEs were considered as non-responders (transfusion avoidance=No).

- Withdrawal from treatment or lost to follow-up before the 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. Phlebotomy/venesection was not included) during the double-blind period.
- Transfusion from Week 5 to Week 24 (Day 29 until end of double-blind period).

Transfusions before Week 5 (Day 29) were not counted and not considered an ICE but patients who withdrew or used prohibited medications before Week 5 were considered non-responders (transfusion avoidance=No).

9.7.3.2.1.3. Change from Baseline to Week 24 in the FACT-An score

The change from Baseline to Week 24 in the FACT-An scores was 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-Roger method to calculate the degrees of freedom. The difference between treatment groups was estimated, along with its 95% CI and p-value.

The FACT-An total score was a key secondary endpoint. Summarized scores included physical, social, emotional, functional, and anemia subscores.

The ICEs and their associated strategies to handle them, were the same as for the key secondary endpoint of change from Baseline to Week 24 in Hb level described in Section 9.7.3.2.1.1. A (descriptive only) summary table of change from Baseline irrespective of ICEs (i.e., with all patient records regardless of whether or not an ICE occurred) were created for FACT-An.

9.7.3.2.2. Other Secondary efficacy endpoint analysis

9.7.3.2.2.1. Secondary efficacy endpoint analyses for Part A

All secondary efficacy analyses were analyzed with the ITT set.

- Number of PRBC transfusions from Week 5 to Week 24

The number of PRBC transfusions from Week 5 to Week 24 in each treatment group was compared using a stratified Wilcoxon rank-sum test p-values. Patients who withdrew from randomized treatment or received prohibited medication before Week 24 had the number of transfusions estimated based on the duration that they were in the study until withdrawal or initiation of prohibited medication.

- Change from Baseline at Week 24 in LDH, haptoglobin, indirect bilirubin, ARC, and D-dimer

The change from Baseline to Week 24 in LDH, haptoglobin, indirect bilirubin, ARC, and D-dimer was 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 to calculate the degrees of freedom. The difference between treatment groups was estimated, along with its 95% CI and p-value.

The ICEs and their associated strategies to handle the data following the ICEs, were the same as for the key secondary endpoint of change from Baseline to Week 24 in Hb level, described in Section 9.7.3.2.1.1. Additional descriptive summary tables of change from Baseline irrespective of ICEs were created for LDH, haptoglobin, ARC, and indirect bilirubin.

Central laboratory values were used for the endpoint assessments discussed above, except ARC which was assessed locally.

- Normalization of markers of hemolysis (LDH, indirect bilirubin, and ARC) at Week 24

A parameter met the normalization response criteria when a patient had an abnormal laboratory result at Baseline, which later improved to normal range post-baseline, as defined by the laboratory data. For the normalization of markers of hemolysis (LDH, indirect bilirubin, and ARC) at Week 24, the number and percentage of patients who achieved normalization was tabulated by treatment group and compared between treatment groups using an exact CMH test stratified for the following strata (≥1/0 transfusions during the 6-month period prior to randomization). The strategy for handling ICEs was the same as for the primary endpoint where patients meeting an ICE were considered as not normalized.

If data at Week 24 was missing, the patient was to be considered not normalized.

A composite strategy for handling of ICEs was used for these endpoints. If any of the ICEs listed below occurred, the patient was not considered normalized at Week 24 and was set to non-responder.

  - 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. Phlebotomy/venesection was not included).
  - Transfusion from Week 5 to Week 24.

Kaplan-Meier plots were generated for the time-to-event endpoints, specifically the time to first normalization from Baseline to Week 24 for LDH, Hb, indirect bilirubin, and ARC for each treatment group at Week 24. Additionally, Kaplan-Meier (median survival) estimates were provided.

Central laboratory values were used for the endpoint assessments discussed above, except ARC that was assessed locally.

- Number of units of PRBCs transfused from Week 5 to Week 24

The number of units of PRBCs transfused from Week 5 to Week 24 in each treatment group was compared using a stratified Wilcoxon rank-sum test (i.e., the Van Elteren test). Patients who withdrew before Week 24 had the number of units estimated from the duration that they were in the study until withdrawal or initiation of prohibited medication.

- Change from Baseline at Week 24 in SF-12, EQ-5D-5L and the FACIT-F subscale score of the FACT-An scale

The change from Baseline at Week 24 in SF-12, EQ-5D-5L and FACIT-F subscale scores of the FACT-An scale was 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 to calculate the degrees of freedom. When the unstructured model failed to converge, other covariance models (autoregressive 1 and compound symmetry) were attempted. The difference between treatment groups was estimated, along with its 95% CI and p-value.

The ICEs and their associated strategies to handle them, were the same as those for the key secondary endpoint of change from Baseline to Week 24 in Hb level described in Section 9.7.3.2.1.1. Additional descriptive summary tables of change from Baseline irrespective of ICEs were created for SF-12, EQ-5D-5L, and the FACIT-FF subscale score of the FACT-An scale.

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

SF-12 summary showed two separate composite scores (Mental Component Score and Physical Component Score) as provided by QualityMetrics.

For EQ-5D-5L, the visual analogue score and each of the 5 dimensions were summarized.

For the FACIT-F score, the total score was summarized as well as the percentage of patients with at least a 4-point improvement from Baseline at Weeks 24 and 48.

The summarized FACT-An scores included the total score and subscores for physical, social, emotional, functional, and anemia.

9.7.3.2.2.2. Secondary efficacy endpoint analysis for Part B

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

- Change from Baseline to Week 48 in Hb, LDH, haptoglobin, indirect bilirubin, ARC, and D-dimer levels

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

- Normalization of markers of hemolysis (LDH, indirect bilirubin, and ARC) at Week 48

The number and percentage of patients who respond were to be tabulated in frequency tables by randomized treatment group in Part A as well as combined. All data were to be used as collected (no ICEs were to be considered) and no imputations were to be done.

- Durability of response

Durability of response was defined as the time until response was lost; loss of response at the first time point when the average change from Baseline in Hb was <1.5 g/dL (the average of all time points starting from Week 24) or the patient received a transfusion or the patient discontinued treatment or the study, or the patient received prohibited medication. Durability of response was to 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 were to be included in this analysis. The time to event was defined as the time the patient achieved the primary endpoint at Week 24 until the earliest time durability of response (as defined above) was lost.

- Change from Baseline to Week 48 in FACT-An, FACIT-F subscale, SF-12, and EQ-5D-5L scores

The change from Baseline at Week 48 in FACT-An, SF-12, EQ-5D-5L, and FACIT-F subscale scores of the FACT-An scale were analyzed using descriptive statistics.

All data were used as collected (no ICEs were considered) and no imputations were done.

9.7.3.2.3. Tertiary efficacy endpoint analysis for Part C

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

- Change from Baseline to Week 96 in Hb, LDH, haptoglobin, indirect bilirubin, ARC, and D-dimer levels

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

- Normalization of markers of hemolysis (LDH, indirect bilirubin, and ARC) at Week 96

The number and percentage of patients who responds was to be tabulated in frequency tables by randomized treatment group in Part A as well as combined.

- Change from Baseline to Week 96 in FACT-An, FACIT-F subscale, SF-12, and EQ-5D-5L scores

The change from Baseline at Week 96 in FACT-An, SF-12, EQ-5D-5L, and FACIT-F subscale scores of the FACT-An scale were to be analyzed using descriptive statistics.

All data were to be used as collected (no ICEs were to be considered) and no imputations were to be done.

Refer to Section 9.8.2 for details on the modifications made to the study conduct due to the premature termination of the study.

9.7.4. Safety Analyses

All safety analyses were carried out descriptively on the Safety set and presented by treatment group.

9.7.4.1. Adverse Events

Pretreatment AEs were those occurring between ICF signature and the first IMP administration. TEAEs were those AEs that started on or after the first dose of IMP and up to 8 weeks after the last dose of study medication. AEs were coded based on the Medical Dictionary for Regulatory Affairs (MedDRA) Version 27.1, September 2024.

AEs were summarized by the number and percentage of patients experiencing AEs. When calculating the incidence of AEs, each AE was counted only once for a given patient within a MedDRA category (e.g., overall, system organ class, or preferred term). When AEs were summarized within levels of another AE assessment (e.g., relatedness or severity), AEs were counted once per patient at the worst level of the assessment (e.g., strongest relationship to IMP or greatest severity).

Exposure adjusted incidence rates were calculated as (number of patients with AE/total person-years at risk)*100. The time at risk per patient was defined as time from first dose of IMP to last dose of IMP + 56 days (treatment-emergent), or death, if earlier, for those patients without a respective TEAE. For patients with a TEAE, time at risk was defined as the time from first dose of IMP to TEAE start date.

Any AE that resulted either in death, was life-threatening, required in-patient hospitalization or led to prolongation of hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was medically important were considered as SAEs. Treatment-emergent SAEs were summarized by preferred term. Refer to Section 9.5.2.1.7 for more details on the SAEs.

All AE data were presented in a listing and included at least onset date, duration, relationship to IMP, relationship to device, severity, action taken with IMP, treatment of event, and outcome.

9.7.4.2. Laboratory Tests

Laboratory data were graded for severity using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and all results of Grade ≥3 were considered clinically meaningful.

The data were presented in a table to summarize patients with CTCAE grading ≥3 from Baseline until 8 weeks after EOT for each laboratory parameter for hematology, chemistry, and urinalysis.

Laboratory parameters (detailed in Table 9-1) are summarized using descriptive statistics and change from Baseline for all laboratory parameters. Baseline was taken as the last measurement prior to the first dose of the IMP.

All laboratory data are presented in a by-patient listing and values outside normal range were flagged.

9.7.4.3. Physical Examination

Physical examination results were described in by-patient listings.

9.7.4.4. Vital Signs

Vital signs were to be graded for severity using the CTCAE v5.0, with Grade ≥3 considered clinically significant. However, all vital sign data including the overall interpretation (Normal and if Abnormal-clinically significant or not clinically significant/Not Evaluable/Not Done) as assessed by the investigator are presented in a by-patient listing.

Summary statistics are presented to describe the clinically meaningful abnormalities as recorded from treatment start date until 8 weeks after EOT for each parameter.

Vital signs are presented with descriptive statistics and change from Baseline for all parameters.

9.7.4.5. Electrocardiograms

Data are presented to summarize the normal, abnormal but not clinically significant, and abnormal clinically significant ECGs recorded at each visit.

All ECG data were presented in a by-patient listing.

9.7.4.6. Immunogenicity Data

Statistical summary tables are presented to summarize the presence of ADA directed against PEG and pegcetacoplan peptide moiety at each visit where immunogenicity was assessed.

ADA evaluable patients were defined as:

- Baseline ADA: having at least one evaluable ADA sample at Baseline
- Treatment-emergent ADA (TEADA) and treatment-boosted ADA (TBADA): having at least one evaluable ADA sample at Baseline and at least one evaluable post dose sample.

Definitions of Baseline ADA prevalence, post-baseline ADA incidence, TEADA, transient treatment-emergent ADA, persistent treatment-emergent ADA, and TBADA are provided in the SAP.

Testing for NAb was performed for all samples with positive ADA anti-pegcetacoplan peptide. Definitions for Baseline NAb prevalence post-baseline NAb incidence, treatment-emergent NAb, and treatment-boosted NAb were the same as for ADA but with NAb.

A summary table of Baseline ADA prevalence, post-baseline ADA incidence, treatment-emergent/boosted ADA, maximum titers for patients with treatment-emergent/boosted ADA, time to treatment-emergent/boosted ADA, duration of treatment-emergent ADA, and the proportion of patients with transient and persistent treatment-emergent ADA are presented for ADA anti-pegcetacoplan peptide and anti-PEG. Additionally, summary tables for Baseline NAb prevalence, post-baseline NAb incidence, and prevalence of treatment-emergent/boosted NAb are presented for antibodies to pegcetacoplan peptide.

Spaghetti plots of individual ADA titers are presented for ADA anti-pegcetacoplan peptide and ADA anti-PEG in semi-logarithmic format.

All immunogenicity data are presented in a by-patient listing.

9.7.5. Exploratory Endpoint Analysis

The exploratory endpoints were to be summarized with numerical descriptive statistics.

- Pegcetacoplan 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

The following endpoint was summarized with frequencies via counts and percentages.

- Normalization of haptoglobin level at Week 24, Week 48, and Week 96.

The following endpoint was summarized with survival estimates in a table.

- Time to first normalization from Baseline to Week 24 for haptoglobin level.

9.7.6. PK and PD Endpoint Analysis

PK/PD analyses and selected PK/PD summaries included in analyses are described in this section.

9.7.6.1. PK Summaries

Pegcetacoplan trough concentrations were evaluated using the PK set. Concentrations were summarized by visit using descriptive statistics. Individual patient concentration-time data were plotted against nominal sampling time and presented as Spaghetti plots. Individual patient concentration time data were also plotted with patients who were positive for ADA and indicated with a different color. Median profiles of the concentration-time data, using nominal sampling times, were also presented. Both linear-linear and semi-log plots were presented.

See Section 11.3.1 for PK concentration results observed during this study.

9.7.6.2. PD Summaries

The PD endpoints were evaluated using the PD set. Absolute values, changes from Baseline and percentage changes from Baseline were summarized using descriptive statistics, over time by treatment group. Individual patient time profiles were plotted against actual sampling time. Median profiles, over time, using nominal sampling time, are also presented.

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

- 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.

See Section 11.3.2 for the results of the PD analyses.

9.7.7. Extent of Exposure

The duration of treatment was defined as the date of last dose of treatment – date of first dose of treatment + 1.

Summary statistics for the duration of treatment, study treatment compliance, and number of infusions received for patients were presented in the Safety set.

The following parameters were calculated and presented using the Safety set:

- Total dose administered (mg)
- Duration of treatment (days)
- Number and percentage of patients who received infusions
    - Number and percentage of patients with all infusions completed

  - Number and percentage of patients with any infusion interrupted
- Total number of infusions
- Number and percentage of infusions completed
- Number and percentage of infusions interrupted

Duration of treatment, study treatment compliance, and number of infusions were presented in a by-patient listing.

9.7.8. Prior and Concomitant Medications

Prior medications refer to any medications administered within 12 weeks prior to obtaining informed consent. Concomitant medications refer to any medications taken after obtaining informed consent. Hence medications started before informed consent but continuing after were considered as both prior and concomitant medications. The listing of medications identifies prior and concomitant medications.

Separate data summary was provided for prior and concomitant medications in the Safety set, presenting the number and percentage of patients by each treatment group.

All prior and concomitant medications were coded using the latest version of World Health Organization drug dictionary (WHO Drug Global, Version September 2024).

Medications were presented by Anatomical Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 5 (standardized medication name) with numbers and percentages by treatment group and overall. A patient who took more than one medication was counted only once if those medications belonged to the same extended ATC classification.

9.7.9. Interim Analysis

No interim analyses were conducted.

9.7.10. Determination of Sample Size

The primary endpoint was response to treatment at Week 24. Under the assumption that the response rate was 55% for pegcetacoplan and 10% in placebo, 54 patients (36 treated with pegcetacoplan and 18 with placebo) were 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 a maximum of 5% non-evaluable patients (i.e., potential missing assessments and drop out prior to first dose of IMP, 57 patients were planned to be enrolled. However, the study was terminated early and only 24 patients were randomized in the study.

9.8. Changes in the Conduct of the Study or Planned Analyses

9.8.1. Changes to the Conduct of the Study

The clinical study protocol was amended 7 times as described in Table 9-2.

Table 9-2. Changes to the Conduct of the Study

Version Number (Date)	Changes
Version 1 (02 August 2021)	Original protocol
Version 2 (08 October 2021)	This amendment included the following changes to the clinical study protocol version 1.0, dated 02 August 2021. • Addition of patient stopping criteria. • Addition of study stopping criteria. • Change of stratification definition regarding prior transfusions. • Removal of the requirement to have a prior rituximab-based therapy. • Change of inclusion criterion regarding liver dysfunction. • Addition of a subgroup analysis on rituximab-experienced/naïve patients for primary and key secondary endpoints. • Change of the instructions for documentation of temperature control of the study drug at the patient's residence.
Version 3 (10 December 2021)	This protocol amendment serves to remove the exploratory measurements of activity/movement by the use of Actigraphy at Baseline, Week 24 and Week 48. In addition, C3 deposition on red blood cells (RBCs) by flow cytometry, which was already included in the study protocol as an assessment, was also described among exploratory endpoints. This protocol amendment also includes the following non-substantial changes/clarifications: • A Principal Coordinating Investigator has been appointed for the study and has been added as protocol signatory. • Addition of wording about course of action at the end of study. • Addition of wording regarding cold agglutinin disease (CAD) history including all prior lines of therapy to be collected as part of the medical history. • Addition of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) among the hematology parameters. • Specification that genetic mutation testing of the MYD88 gene will be performed locally for patients requiring a bone marrow biopsy for study purposes. • Corrections in the description of the statistical analysis of secondary endpoints. • The version of the 12-Item Short Form Survey in Appendix 3 has been replaced. In addition to the above-mentioned changes, minor typos were corrected.

Japan addendum to protocol version 3 (07 April 2022)	This Japan-specific protocol addendum for Sobi.PEGCET-101 was prepared to account for country-specific requirements on some study procedures, in accordance with the approach that had been implemented in the pegcetacoplan protocols for the paroxysmal nocturnal hemoglobinuria (PNH) program. This addendum covers the following 4 considerations: • The acceptable contraceptive methods described for Study Sobi.PEGCET-101 include implantable contraceptives, injection and removable contraceptives. These contraceptive methods are not approved in Japan and, therefore, will be prohibited in Study Sobi.PEGCET-101 in Japan. • Because the type B meningococcal vaccine described in the protocol is not approved in Japan, Japan is not an endemic area of meningitis caused by type B Neisseria meningitidis, and meningitis derived from type B N. meningitidis has been decreasing in recent years, the clinical study in Japan will not use type B meningococcal vaccine. • Study Sobi.PEGCET-101 permits infusions by caregivers at home. However, this does not comply with the Medical Practitioners' Act in Japan requirements specifying that the study drug can be injected only by a qualified person such as a physician, or in the case of home self-injection only by the patient or a home nurse. In addition, there are no provisions that allow caregivers to inject study drugs in Japan. • The package insert of pneumococcal vaccine (PPSV23: Pneumovax NP) describes, "It has been reported that adverse reactions including pain, erythema, and induration at the injection site were more frequently found than the initial vaccination in those who had been vaccinated with polyvalent pneumococcal capsular polysaccharide vaccine within the past 5 year. When this product is re-inoculated, carefully consider the need for re-inoculation and ensure a sufficient interval from the previous inoculation." Therefore, specific wording was added to the protocol on pneumococcal vaccine adverse reactions to alert the investigators before the conduct of this clinical study. **Note**: This version of the protocol was not submitted to PMDA due to an issue with the vaccination schedule. Therefore, Protocol v4.0 Japan addendum_21 June 2022 was submitted along with a clarification letter.

Global protocol version 4 (28 April 2022) and Japan addendum to global protocol v4.0 (21 June 2022)	This amendment to the protocol adds the following inclusion and exclusion criteria: <u>Added inclusion criterion</u> • An absolute neutrophil count ≥1500 cells/mm^3 at Screening. <u>Added exclusion criteria</u> • Protected adults (guardianship, trusteeship) who are unable to express their consent and persons under court protection. • Hypersensitivity to pegcetacoplan or to any of the excipients or placebo compounds. • Unresolved infection caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. • Known or suspected hereditary fructose intolerance. The study endpoints were modified as follows: • The key secondary endpoints were displayed in a different order. • For Hb, LDH, indirect bilirubin, ARC and haptoglobin levels, only time to first normalization from Baseline to Week 24 will be measured, and time from Baseline to Weeks, 48 and 96 was removed. • Addition of separate analysis of the subset of questions in the FACIT-Fatigue scale. In addition, the exploratory objective to evaluate change in patient activity level and energy expenditure has been removed. This protocol amendment also includes the following changes/clarifications: • Addition of definition of durability of response. • Clarification of wording regarding mandatory antibiotic prophylaxis. • Revision of the emergency unblinding process. • Clarification that administration of COVID-19 vaccine was allowed during the study. • Clarification of clinically meaningfulness for the laboratory data and vital signs. • Clarifications on the description of analyses of primary and secondary endpoints. • Addition of wording about patients' treatment in case of early study termination by the sponsor. • Addition of severe hypersensitivity reaction as a condition leading to immediate and permanent discontinuation of study treatment. • Update of potential risks and benefits assessment. • Increase of the safety follow-up period from 6 to 8 weeks after the last IMP dose; increase of the pregnancy follow-up period from 6 weeks to 90 days. • Change of frequency of urine pregnancy tests so these are performed every 4 weeks throughout the study.

	• Change of consideration of urine pregnancy tests as part of the minimum study requirements in case of COVID-19 restrictions. • Clarification that for self-administration the patient can come more frequently to sites for IMP administration and training on how to use the pump. • Correction of sentence in the study rationale section. In addition to the above-mentioned changes, minor typos have been corrected, including deletion of X's in the schedule of assessments for inflammatory biomarkers in Part C.
Global protocol version 5 (13 March 2023) and Japan addendum to global protocol v5.0 (version 1.0, 13 March 2023)	• Inclusion criteria was adjusted to clarify: o It was noted that the diagnosis of primary cold agglutinin disease (CAD) should be on the basis of the presence of all the criteria at Screening. o The restriction that patients who were not previously vaccinated should not receive multiple vaccines on the same day was removed and replaced with a reminder that vaccinations should be administered following the Advisory Committee on Immunization Practices (ACIP) recommendations for adults or children with complement deficiencies and/or immunocompromising conditions, as was already noted elsewhere in the protocol. • Exclusion criteria was adjusted to clarify: o The exclusion period for sutimlimab was changed from within 4 weeks prior to randomization to within 15 weeks prior to randomization. Patients previously treated with >1 dose of sutimlimab but who have not had experienced a documented increase in hemoglobin (Hb) ≥ 1.0 g/dL during sutimlimab treatment was added as exclusionary. o Belimumab and anti-CD20 antibody other than rituximab were added as exclusionary treatments, and the exclusionary period from other treatments, as monotherapy or in combination, had been set to 16 weeks prior to randomization. o For diagnosis of systemic lupus erythematosus or other autoimmune diseases with antinuclear antibodies, it was noted that antinuclear antibodies of long-standing duration without associated clinical symptoms will be adjudicated on a case-by-case basis. o For cold agglutinin syndrome secondary to Mycoplasma pneumoniae, Epstein-Barr virus or other specific causative infection, it was added that patients with long history of CAD, positive IgM titer and IgG titer without associated clinical symptoms will be adjudicated on a case-by-case basis. o For liver dysfunction, it was noted that for any patient with increased direct bilirubin, the investigator should exercise his judgement to ensure that the increased direct bilirubin value was due to hemolysis and discuss inclusion with the medical monitor. If the direct bilirubin was higher than the indirect bilirubin, in addition a thorough search for exclusion of underlying liver or cholestatic disease, including but not necessarily limited to abdominal ultrasound, was warranted to exclude liver and/or cholestatic disorders.

	○ Any infection (including coronavirus disease 2019 [COVID-19]) requiring hospitalization or treatment with intravenous anti-infectives not resolved within 2 weeks prior to the first dose of the investigational medicinal product (IMP) was added as exclusionary. • It was clarified that the screening assessments that were to be performed within 1 week prior to randomization were requested to be performed prior to dosing on Day 1 or, if convenient for the patient and/or the site due to logistic reasons, may be performed the day before first IMP dosing; randomization may also occur the day before first IMP dosing. Some Baseline assessments may be performed by the local laboratories to ensure availability of the results before the first IMP dosing. Also, the 4-week Screening period may be extended by 2 additional weeks if needed and after consultation with the medical monitor (e.g., eligibility laboratory results not available due to technical reasons or the patient receives a red blood cell (RBC) transfusion during the last week of the Screening period, reasonably reversible medical reasons such as COVID-19 infection). • Revision of some assessments during the study. • Clarification that if a patient experiences acute hemolytic crisis and receives blood cell transfusions during the Screening period, the start of dosing must occur at least 7 days after receiving last transfusion. • Clarification of the pre-dose PK samples will be taken within 15 min before the administration of the study drug and strictly before the start of dosing. • Allowance to use local laboratory or historical data for Screening direct antiglobulin test (DAT) testing and reduction of testing timepoints during the study. • Clarification of management of patients in case pegcetacoplan was not commercially available at the end of Part C. • Clarification about retesting and rescreening procedures. • Addition of criteria for premature termination of the study. • Removal of bortezomib and belimumab from list of permitted concomitant medications, with the former added as prohibited medication, and the latter implicitly excluded under other investigational drug for this condition. It was clarified that phlebotomy/venesection for iron overload was only prohibited during Part A. • Addition of IMP blinding details to the investigators and sponsor regarding certain laboratory data could potentially hint at treatment assignment. • Addition of serious adverse event (SAE) reporting for screen failures. • Revision of Baseline definition: the last measurement during the Screening, prior to the first dose of IMP. In addition, this definition had been added to the Section General statistical issues and removed elsewhere. • Other clarifications in the statistical section, including updated details of the determination of sample size, the method used for the analysis of the primary objective, definition of durability of

	response or wording related to handling of intercurrent events (ICEs), analysis method. • Change of Sponsor's Medical Director.
Japan addendum to global protocol v5.0 (version 2.0, 13 March 2023)	Added 'Attachment 1: Nonapproved Medical Devices Reporting Requirements' to Japan protocol addendum v1.0.

Source: Protocol summaries of changes (Appendix 16.1.1).

9.8.2. Changes in the Planned Analyses

The SAP version 2.0 was finalized based on protocol version 5.0 (13 March 2023) in October 2024, after the decision to terminate the study. In the event of any discrepancies between the protocol and the SAP, the SAP takes precedence.

Below are the changes in the planned analyses (as documented in SAP V2.0) that occurred due to premature termination of the study:

- Enrolled only 24 patients instead of planned number of 57 patients.
- Subgroup analyses were limited to primary efficacy and key secondary efficacy endpoints for Part A only.
- Planned frequency tables for the proportion of patients who achieved normalization of markers of hemolysis (i.e., ARC, indirect bilirubin, LDH, and haptoglobin) were not included for Parts B and C. Only the proportion with normalization at Week 24 was presented for Part A.
- Durability of response (during Part B) was not analyzed.
- None of the planned statistical analyses for Part C or sensitivity analyses were performed.

In addition, the following analyses were specified in Protocol version 5.0 but not included in the SAP when it was finalized after the decision to terminate the study.

- Sensitivity analyses for the primary endpoint using the PP and mITT analysis sets were omitted from the SAP.

9.8.3. Changes Following Study Unblinding and Post-hoc Analyses

After unblinding, it became obvious that the policy for imputing below limit of quantification (BLQ) PK concentrations outlined in the SAP was not specific enough. The SAP refers to imputing BLQ results to 0 before “treatment” and to the lower limit of quantification after treatment. However, this should have been “treatment with pegcetacoplan” and the analysis was conducted as such.

After unblinding, the mock shells were found to lack two expected listings to present the complement biomarker/flow cytometry data and the inflammatory biomarker data. These were added as Listings 16.3.1 for complement biomarker/flow cytometry and 16.3.2 for inflammatory biomarkers.

The planned presentation of LS Means in Figure 14.2.12.2 was not possible on account of model non-convergence. A decision was made post hoc to instead present the arithmetic means in this figure.

10. STUDY SUBJECTS

10.1. Patient Disposition

The disposition of patients in All Screened Patients is summarized in Figure 10-1. Summary of the patients' disposition in All Screened Patients is presented in Table 14.1.1. A by-patient listing of disposition in the Safety set is provided in Listing 16.2.1.

A total of 38 patients were screened, with 14 patients failing screening. Of the 24 patients eligible for the study, 16 patients were randomized to pegcetacoplan and 8 patients to placebo. Overall, 21 patients (87.5%) completed the double-blind treatment period (Part A) and 11 patients (45.8%) completed the open-label treatment period (Part B). None completed open-label maintenance period (Part C).

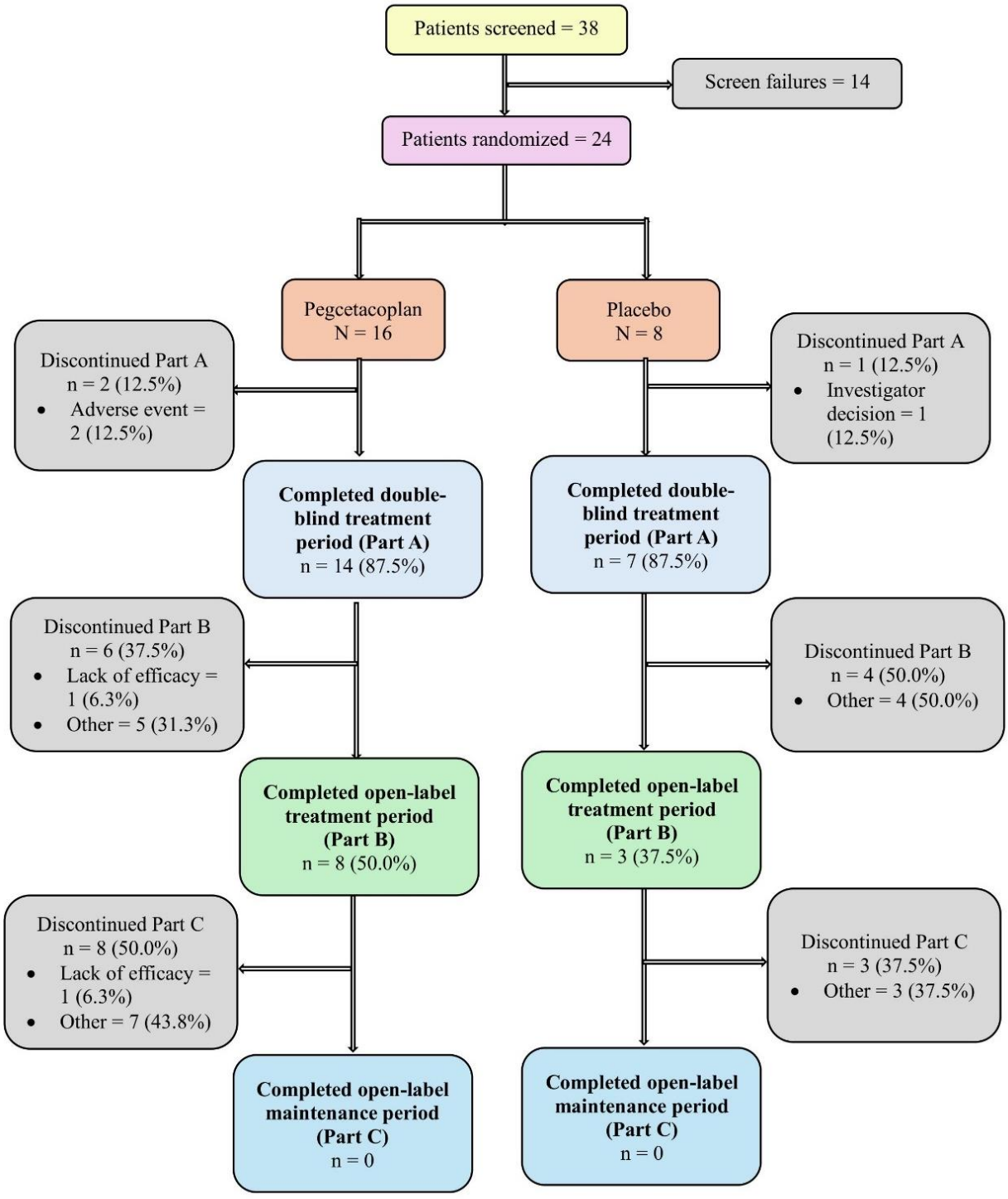
In Part A, 3/24 patients (12.5%) discontinued IMP due to AEs (2 patients [12.5%] in the pegcetacoplan group) and investigator decision (1 patient [12.5%] in the placebo group). In Part B, 10/24 patients (41.7%) were discontinued, with majority of them (9/24 patients [37.5%]) listed other reasons for their discontinuation. In Part C, 11/24 patients (45.8%) were discontinued, with majority of them (10/24 patients [41.7%]) listed other reasons for their discontinuation. The most common reason among "other" causes for premature discontinuation of the IMP was the sponsor's decision to terminate the study.

Notes:

One of the 3 patients (Patient 440102) who prematurely discontinued the IMP due to a TEAE of Cholecystitis (onset date of 28 Jul 2023) (per Table 14.3.1.8) was not counted under the reason for early termination of 'Adverse Event' (in Table 14.1.1) in this section, as the TEAE that led to IMP and study discontinuation was fatal (TESAE of Cholecystitis). However, in the Section 12, the same TESAE of Cholecystitis was counted as one of TEAEs that led to IMP discontinuation.

The study was terminated early due to enrollment challenges arising from a decreased medical need for pegcetacoplan in CAD, i.e., limited number of patients available to participate in the study. At the time of the decision to terminate the study, all the patients who were ongoing were allowed to stay on treatment until 10 July 2024 to move out of the cold season and have appropriate time to transition to alternative treatment.

Figure 10-1. Summary of Patient Disposition (All Screened Patients)



Source: Table 14.1.1.

10.2. Protocol Deviations

A summary of protocol deviations is provided in Table 14.1.3. All protocol deviations are listed by patient in Listing 16.2.2.

In Part A, 189 protocol deviations were reported in 24 patients, with 46 of them being categorized as major deviations. Most of the major protocol deviations in Part A were observed in the pegcetacoplan group when compared with the placebo group (27 versus 19 major deviations). Missed assessment or incorrect procedure and other reasons accounted for the highest percentage of patients with major protocol deviations (7/24 patients [29.2%] in each category), followed by incorrect treatment schedule (5/24 patients [20.8%]). In Parts B and C collectively, a total of 28 major protocol deviations were noted in 21 patients. Majority of these deviations was due to incorrect treatment schedule, reported in 5/21 patients (23.8%).

10.3. Data Sets Analyzed

Table 10-1 summarizes the population assignment. All the 24 patients, who were randomized during the study, were included in Safety, ITT, PK, and PD sets. The Per Protocol set was not included in the analysis, see Section 1.1 of the Statistical Analysis Plan V2.0.

Table 10-1. Summary of Population Assignment

Patient Disposition	Pegcetacoplan (N=16) n (%)	Placebo (N=8) n (%)	Total (N=24) n (%)
Safety Set	16 (100%)	8 (100%)	24 (100%)
ITT Set	16 (100%)	8 (100%)	24 (100%)
PK Set	16 (100%)	8 (100%)	24 (100%)
PD Set	16 (100%)	8 (100%)	24 (100%)

Source: Table 14.1.1.

ITT = intent-to-treat; PD=pharmacodynamic; PK=pharmacokinetic.

Note: The table above presents data for randomized patients instead of all screened patients as reported in the source Table 14.1.1.

10.4. Demographic and Other Baseline Characteristics

10.4.1. Demographics

A summary of key demographics and Baseline characteristics by treatment group for the Safety set is provided in the Table 10-2. All demographic characteristics by treatment group for Parts A and B are presented in Table 14.1.2. Demographic data by patient is provided in Listing 16.2.4.

Patients initially assigned to pegcetacoplan and to placebo had overall comparable demographic characteristics. No patients with childbearing potential were included in the study.

As expected from the general characteristics of the CAD patient population, most study patients were elderly with a median age at study entry of 73.5 years and ages ranging from 59 to 84 years.

Table 10-2. Summary of Selected Demographics and Baseline Characteristics – Safety Set

Characteristics	Part A			Part B
	Pegcetacoplan (N=16)	Placebo (N=8)	Total (N=24)	Total (N=21)
Age (years)				
n	16	8	24	21
Mean (SD)	74.8 (7.25)	71.9 (6.73)	73.8 (7.08)	73.4 (7.16)
Median	76.0	73.0	73.5	73.0
Min, Max	64, 84	59, 82	59, 84	59, 83
Sex [n (%)]				
Male	6 (37.5%)	2 (25.0%)	8 (33.3%)	7 (33.3%)
Female	10 (62.5%)	6 (75.0%)	16 (66.7%)	14 (66.7%)
Race [n (%)] [1]				
White	12 (75.0%)	8 (100%)	20 (83.3%)	17 (81.0%)
Black or African American	0	0	0	0
Asian	4 (25.0%)	0	4 (16.7%)	4 (19.0%)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian/Other Pacific Islander	0	0	0	0
Not Applicable	0	0	0	0
Not Reported	0	0	0	0
Other	0	0	0	0
Ethnicity [n (%)]				
Hispanic or Latino	1 (6.3%)	0	1 (4.2%)	0
Not Hispanic or Latino	15 (93.8%)	8 (100%)	23 (95.8%)	21 (100%)
Not Reported	0	0	0	0
Unknown	0	0	0	0
Screening Body Mass Index (BMI) (kg/m^2)[2]				
n	16	8	24	21
Mean (SD)	23.84 (4.015)	25.16 (2.848)	24.28 (3.658)	24.61 (3.798)
Median	22.85	26.41	24.13	25.40
Min, Max	18.1, 35.2	21.1, 28.4	18.1, 35.2	18.1, 35.2

Source: Table 14.1.2.

Notes:

[1] Multiple values for race may be reported for a patient.

[2] BMI was defined as (Weight [kg] / [Height {m}]^2).

BMI=body mass index; max=maximum; min=minimum; SD=standard deviation.

10.4.2. Other Baseline Characteristics

10.4.2.1. Disease History

A summary of patients targeted medical history is provided in Table 10-3. Targeted medical history is presented by treatment group in Table 14.1.4.2 and by patient is provided in Listing 16.4.2.

Patients' targeted medical history was overall comparable, other than for marginally higher proportions of patients in the pegcetacoplan group with reduced haptoglobin or prior hospitalization due to CAD, a higher proportion of patients in the pegcetacoplan group with elevated indirect bilirubin or noticeable symptoms; history of prior non-malignant hematologic disease and warm autoimmune hemolytic anemia being noted in one patient each, both in the pegcetacoplan group; prior thromboembolic history and myocardial infarction being noted in one patient each, both in the placebo group; and a higher proportion of patients who have received prior rituximab-based treatment in the placebo group.

Table 10-3. Summary of Targeted Medical History – Safety Set

Medical History	Part A			Part B
	Pegcetacoplan (N=16)	Placebo (N=8)	Total (N=24)	Total (N=21)
Time since diagnosis (years)				
n	16	8	24	21
Mean (SD)	6.0 (5.09)	7.0 (8.60)	6.3 (6.30)	6.1 (6.56)
Median	4.5	4.3	4.5	4.5
Min, Max	1, 18	0, 26	0, 26	0, 26
Patients with signs of hemolysis with abnormal values of at least 2 hemolytic markers [n (%)]				
Yes	16 (100%)	8 (100%)	24 (100%)	21 (100%)
Reduced haptoglobin level [1]				
Yes	14 (87.5%)	6 (75.0%)	20 (83.3%)	17 (81.0%)
Elevated LDH level [1]				
Yes	14 (87.5%)	7 (87.5%)	21 (87.5%)	18 (85.7%)
Elevated indirect bilirubin level [1]				
Yes	13 (81.3%)	4 (50.0%)	17 (70.8%)	15 (71.4%)
Increased ARC [1]				
Yes	8 (50.0%)	4 (50.0%)	12 (50.0%)	12 (57.1%)
Direct antiglobulin test strongly positive for C3d [n (%)]				
Yes	16 (100%)*	8 (100%)*	21 (87.5%)	18 (85.7%)
Cold agglutinin titer ≥64 at 4C				
Yes	16 (100%)*	8 (100%)*	21 (87.5%)	19 (90.5%)
Symptoms				
Yes	11 (68.8%)	4 (50.0%)	15 (62.5%)	13 (61.9%)
Prior hospitalization due to CAD				
Yes	7 (43.8%)	3 (37.5%)	10 (41.7%)	9 (42.9%)
Prior hematological malignancy history?				
Yes	1 (6.3%)	1 (12.5%)	2 (8.3%)	1 (4.8%)
Low grade/indolent malignancy [2]				
Yes	1 (100%)	1 (100%)	2 (100%)	1 (100%)

Medical History	Part A			Part B
	Pegcetacoplan (N=16)	Placebo (N=8)	Total (N=24)	Total (N=21)
History of prior non-malignant hematologic disease?				
Yes	1 (6.3%)	0	1 (4.2%)	0
Warm autoimmune hemolytic anemia [3]				
Yes	1 (100%)	0	1 (100%)	0
Prior thromboembolic history?				
Yes	0	1 (12.5%)	1 (4.2%)	1 (4.8%)
Myocardial infarction [4]				
Yes	0	1 (100%)	1 (100%)	1 (100%)
Prior rituximab-based treatment?				
Yes	7 (43.8%)	7 (87.5%)	14 (58.3%)	12 (57.1%)
Prior transfusions in the 6 months prior to randomization				
Yes	8 (50.0%)	4 (50.0%)	12 (50.0%)	9 (42.9%)

Source: Table 14.1.4.2.

[1] The denominator was the number of patients with abnormal values of at least 2 haemolytic markers.

[2] The denominator was the number of patients with a prior hematological malignancy. Identified categories (e.g., aggressive lymphoid malignancy) were only assessed among those reporting hematological malignancy.

[3] The denominator was the number of patients with a prior non-malignant hematological disease. Indented categories (e.g., Warm autoimmune haemolytic anaemia) were only assessed among those reporting non-malignant hematological disease.

[4] The denominator was the number of patients with prior thromboembolic history. Indented categories (e.g., stroke) were only assessed among those reporting prior thromboembolic history.

[*] This number differs from the source table as data for 3 patients were not included in the table but alternative evidence of the patients meeting this inclusion criterion is available and filed in note to files and eligibility review forms (for Patients 310201, 320201, and 440103). These documentation have been filed in the electronic Trial Master File.

ARC=absolute reticulocyte count; C3d=complement component C3d; CAD=Cold Agglutinin Disease; LDH=lactate dehydrogenase; max=maximum; min=minimum;- SD = standard deviation.

10.4.2.2. Alcohol Consumption and Smoking History

Table 14.1.4.3 summarizes the patients' alcohol consumption and smoking history by treatment group and total in the Safety set.

A total of 10/16 patients (62.5%) in the pegcetacoplan group reported alcohol consumption, with 6/16 patients (37.5%) consuming alcohol at a moderate level. Seven of 16 patients (43.8%) reported tobacco usage, with an average smoking history of 33 packs/year. In the placebo group, 2/8 patients (25.0%) reported moderate alcohol consumption and tobacco usage with an average

smoking history of 228 packs/year. Alcohol consumption was more common in the pegcetacoplan group, while smoking (packs/year) was higher in the placebo.

10.4.2.3. Bone Marrow Biopsy History

The history of bone marrow biopsy by treatment group and total in the Safety set is provided in Table 14.1.4.4. By-patient details on the bone marrow biopsies are presented in Listings 16.4.17.1 (Part 1) and 16.4.17.2 (Part 2).

The bone marrow biopsy was performed within 12 months prior to the informed consent in 17/24 patients (70.8%; 11/16 patients [68.8%] in the pegcetacoplan group and 6/8 patients [75.0%] in the placebo group) enrolled in the study. Thirteen of 24 patients (54.2%; including 11/16 patients [68.8%] in the pegcetacoplan group and 2/8 patients [25.0%] in the placebo group) had positive results for lymphoproliferative infiltration with a mean (SD) percentage infiltration of 8.8% (5.8; which includes 9.8% [5.6] in the pegcetacoplan group and 3.0 [2.8%] in the placebo group). A low grade/indolent lymphoid malignancy was recorded in 5/24 patients (20.8%) in Part A (with all 5 patients [31.3%] in the pegcetacoplan group and none in the placebo group). The biopsy results also showed other hematologic process in 1/24 patient (4.2%; including 1/16 patient [6.3%] in the pegcetacoplan group and none in the placebo group). The MYD88 mutation test result was positive for 1/24 patient (4.2%; including none in the pegcetacoplan group and 1/8 patient [12.5%] in the placebo group).

10.4.2.4. Vaccination History

Table 14.1.9 summarizes prior vaccination history within 12 weeks prior to informed consent by treatment group and total for the Safety set. A total of 14/24 patients (58.3%) who received pegcetacoplan in any of the three parts of the study had a prior vaccination. Of these, the majority of the patients (11/24 patients [45.8%]) received *S.pneumoniae* vaccine. Four of 8 patients (50.0%) in placebo group of Part A received *S.pneumoniae* vaccine within 12 weeks prior to informed consent before study entry. Refer to Listing 16.4.6 for all prior vaccines taken by the patients.

10.4.3. Medical History

Medical history was collected at Screening for all patients. Medical history summarized by treatment group and total is provided in Table 14.1.4.1. Medical history other than CAD by patient is detailed in Listing 16.4.1.

Some of the commonly reported historical conditions (occurred in >2 patients by preferred term [PT] in each system organ class [SOC]) included Hypertension (10/24 patients [41.7%] enrolled in Part A, including 5/16 patients [31.3%] in the pegcetacoplan group and 5/8 patients [62.5%] in the placebo group), Atrial fibrillation (6/24 patients [25.0%] in Part A, including 5/16 patients [31.3%] in the pegcetacoplan group and 1/8 patient [12.5%] in the placebo group), Constipation (4/24 patients [16.7%] in Part A, including 4/16 patients [25.0%] in the pegcetacoplan group and none in the placebo group), and Jaundice (4/24 patients [16.7%] in Part A, including 4/16 patients [25.0%] in the pegcetacoplan group and none in the placebo group). Hence, there was an overall high prevalence of concomitant conditions as expected in the elderly population recruited in this study.

Hypertension and Constipation are frequent in an older population such as those in this trial, while jaundice is a known effect of hemolytic anemia such as CAD anemia, and Atrial fibrillation is

relatively frequent in older patients and is more frequent in the presence of anemia. While some numerical differences between patients assigned to both treatment arms were observed, their interpretation is difficult due to the small number of patients and they do not appear likely to relevantly influence the study results interpretation.

10.4.4. Prior Medications and Procedures

Prior medications are those medications administered to the patients within 12 weeks prior to providing informed consent. Table 14.1.5.1 illustrates the prior medications by treatment group and ATC Level 2/5 for Safety set. Listing 16.4.3 gives information on prior and concomitant medications by patient in the Safety set.

In Parts A, B, and C, 10/23 patients (43.5%) who received pegcetacoplan and 3/8 patients (37.5%) who received placebo in Part A reported prior medication use. Overall, 9/23 patients (39.1%) who received pegcetacoplan and 3/8 patients [37.5%] who received placebo from Part A reported receiving vaccines. The commonly administered vaccine of all was pneumococcal vaccine polysacch 23V (3/16 patients [18.8%] in the pegcetacoplan group and 1/8 patients [12.5%] in the placebo group). One of 16 patient (6.3%) from Part A – pegcetacoplan group received bile and liver therapy (ursodeoxycholic acid).

Note: Parts A, B, and C overall in the summary tables refer to the total number of patients who received pegcetacoplan during the study, while placebo group of Part A reflects the patients who received placebo during Part A and eventually enrolled into open-label treatment period to receive pegcetacoplan.

Table 14.1.10 describes prior CAD therapy taken by the patients in the Safety set. Overall, for Parts A, B, and C, the mean (SD) time since the last prior CAD therapy was 3.08 years (4.36) for pegcetacoplan patients, while it was 4.42 years (6.6) for placebo patients in Part A. Most of the pegcetacoplan-treated patients (54.2%) and placebo-treated patients (87.5%) received rituximab monotherapy in the past for CAD. Prior CAD therapy by patient is provided in Listing 16.4.7.

Prior procedures refer to any procedures conducted within 12 weeks prior to obtaining consent. Table 14.1.5.3 summarizes prior procedures by treatment group. Listing 16.4.4 details all prior and concomitant procedures by patient. Two of 23 patients (8.7%) from the overall pegcetacoplan group (both were assigned to the pegcetacoplan group) underwent gallbladder removal, magnetic resonance imaging abdomen, and echocardiography before consenting for this study. No patients from the placebo group underwent any prior procedure.

10.4.5. Concomitant Medications and Procedures

Concomitant medications refer to any medications administered from the time of informed consent through the EOS visit. Refer to Table 14.1.5.2 for the concomitant medications taken by all patients in the Safety set during this study. Listing 16.4.3 provides the details of all prior and concomitant medications by patient.

The concomitant medications by ATC Level 2 that were taken most frequently (by ≥50% patients overall) included: vaccines (91.3% pegcetacoplan patients in all parts of study and 87.5% pegcetacoplan patients in Part A versus 100% placebo patients in Part A), antianemic preparations (56.3% pegcetacoplan patients versus 75.0% placebo patients in Part A), drugs for acid related disorders (68.8% pegcetacoplan patients versus 37.5% placebo patients in Part A), analgesics (50.0% pegcetacoplan patients versus 62.5% placebo patients in Part A), antibacterials for

systemic use (56.3% pegcetacoplan patients versus 50.0% placebo patients in Part A), corticosteroids for systemic use (43.8% pegcetacoplan versus 50.0% placebo patients in Part A), antithrombotic agents (37.5% pegcetacoplan versus 62.5% placebo patients in Part A), and agents acting on the renin-angiotensin system (25.0% pegcetacoplan versus 62.5% placebo patients in Part A).

Table 14.1.8 summarizes the prophylactic antibiotics received by the patients. Two of 23 pegcetacoplan patients (8.7%) overall received amoxicillin and levofloxacin (one each), while one of the 8 placebo patients (12.5%) and 0/16 pegcetacoplan patient (0%) in Part A received amoxicillin trihydrate. Prophylactic antibiotics administered by patient is provided in Listing 16.4.5.

Concomitant procedures are those procedures performed from the time of informed consent through the EOS visit. Table 14.1.5.4 summarizes concomitant procedures in the Safety set. Each concomitant procedure recorded during the study was reported in no more than 1 patient receiving pegcetacoplan. Listing 16.4.4 details all prior and concomitant procedures by patient.

10.5. Measurements of Treatment Compliance

A summary of study treatment compliance measurement is provided in Table 10-4. The majority of the patients (22/23 patients [95.7%]) showed ≥90% to ≤100% compliance with pegcetacoplan treatment. Fifteen out of 16/patients (93.8%) showed ≥90% to ≤100% compliance with pegcetacoplan during Part A. Six of 8 patients (75.0%) showed similar compliance with placebo during Part A. One patient (12.5%) showed ≥80% to <90% and another patient (12.5%) showed >100% compliance with placebo in Part A. One patient (4.3%) exceeded 100% compliance with pegcetacoplan in Part A. None reported <80% compliance with any study treatment.

Table 10-4. Summary of Study Treatment Compliance

Characteristic	Part A		Parts A, B, and C
	Pegcetacoplan (N=16) n (%)	Placebo (N=8) n (%)	Overall Pegcetacoplan (N=23) n (%)
Study Treatment Compliance			
<80%	0	0	0
>=80% to <90%	0	1 (12.5%)	0
>=90% to <=100%	15 (93.8%)	6 (75.0%)	22 (95.7%)
>100%	1 (6.3%)	1 (12.5%)	1 (4.3%)

Source: Table 14.1.7.

Note: Study compliance (%)=100 * (total number of infusions)/(total number of infusions planned to be taken).

11. EFFICACY EVALUATION

All efficacy analyses were performed on the ITT set.

11.1. Primary Analysis

11.1.1. Response to Treatment at Week 24

The primary endpoint was response to treatment at Week 24. A summary of the response is presented in Table 11-1. At Week 24, 8/16 patients (50.0%) treated with pegcetacoplan achieved a response, compared with 2/8 patients (25.0%) treated with placebo. No statistically significant difference was observed in the response rates between the two groups (p-value=0.262). Hence, the primary efficacy endpoint of the study was not met.

Table 11-1. Summary of Response to Treatment at Week 24

Characteristic	Pegcetacoplan (N=16)	Placebo (N=8)
Week 24		
Patients achieving a Response [n (%)]	8 (50.0%)	2 (25.0%)
Difference in Response Rate (95% CI)	0.250 (-0.137, 0.637)	
Odds Ratio (95% CI)	3.000 (0.361, 34.277)	
p-value	0.262	

Source: Table 14.2.1.2.

CI=confidence interval.

11.1.1.1. Sub-group Analyses of Response to Treatment at Week 24:

11.1.1.1.1. Transfusion history

Table 14.2.1.3 summarizes the responses to treatment at Week 24 based on transfusion history. In the subgroup of patients who had received at least one transfusion in the prior 6 months, 4/8 patients (50.0%) in the pegcetacoplan group and 1/4 patient (25.0%) in the placebo group achieved a response at Week 24. For the subgroup of patients who did not receive any transfusions in the prior 6 months, the response rates in both treatment arms were identical with those observed in the subgroup that received at least one transfusion during the same period.

11.1.1.1.2. Rituximab history

A summary of responses to treatment at Week 24 based on the rituximab history is provided in Table 14.2.1.4. In the subgroup of patients previously treated with rituximab, 4/7 patients (57.1%) in the pegcetacoplan group achieved a response at Week 24, compared with 2/7 patients (28.6%) in the placebo group. In the subgroup of patients who were not previously treated with rituximab, 4/9 patients (44.4%) in the pegcetacoplan group achieved a response at Week 24, while the single patient in the placebo group did not achieve a response.

11.1.2. Key Secondary Analyses

No formal statistical tests were conducted for any of the study secondary endpoints because it was not allowed by the hierarchical endpoint testing strategy, as defined in the study Protocol for the

control of multiplicity given that the primary endpoint was not met. Hence, the reported p-values are nominal and quoted for purely descriptive purposes.

11.1.2.1. Change from Baseline to Week 24 in Hemoglobin Level (Part A)

Table 11-2 summarizes the change from Baseline to Week 24 (Part A) in Hb level in the absence of ICEs. Table 14.2.2.1 provides a summary of the observed values and change from Baseline in Hb levels for various time points across the study. Figure 11-1 shows the change in the Hb values (using least squares [LS] Mean [standard error {SE}]) from Baseline to Week 24 visit.

For the patients who had Week 24 assessment done, the mean (SD) values for Hb at Baseline were comparable for pegcetacoplan and placebo groups, measuring 8.0 g/dL (1.2) and 8.6 g/dL (0.6), respectively. At Week 24, the observed mean (SD) values were 10.8 g/dL (1.6) and 10.1 g/dL (0.8) in the pegcetacoplan and placebo groups, respectively. The mean (SD) change from Baseline to Week 24 was 2.8 g/dL (1.9) in the pegcetacoplan group and 1.5 g/dL (1.1) in the placebo group. The difference in the LS Mean change from Baseline between the two treatment groups was 1.5 g/dL (95% CI=[0.65, 2.33]) and with a nominal p-value of <.001.

Table 11-2. Summary of Hemoglobin (g/dL) in the Absence of Intercurrent Events – ITT Set

Characteristic		**Pegcetacoplan (N=16)**		**Placebo (N=8)**	
Study Part(s)		**Actual Value**	**Change from Baseline**	**Actual Value**	**Change from Baseline**
Part A	Baseline (Patients with Week 24 Assessment)				
	N	12		5	
	Mean (SD)	8.03 (1.167)		8.62 (0.599)	
	Median	8.40		8.86	
	Min, Max	6.1, 9.9		7.8, 9.3	
	Week 24 [1]				
	N	12	12	5	5
	Mean (SD)	10.78 (1.610)	2.75 (1.905)	10.14 (0.804)	1.53 (1.084)
	Median	10.75	2.80	9.70	1.50
	Min, Max	8.2, 13.2	0.1, 6.4	9.5, 11.4	0.4, 3.2
	LS Mean Estimate (SE)		2.85 (0.306)		1.36 (0.278)
	Diff (Pegcetacoplan - Placebo)				
	LS Mean Estimate (SE)		1.49 (0.413)		
	p-value		<.001		
	95% CI		(0.65, 2.33)		

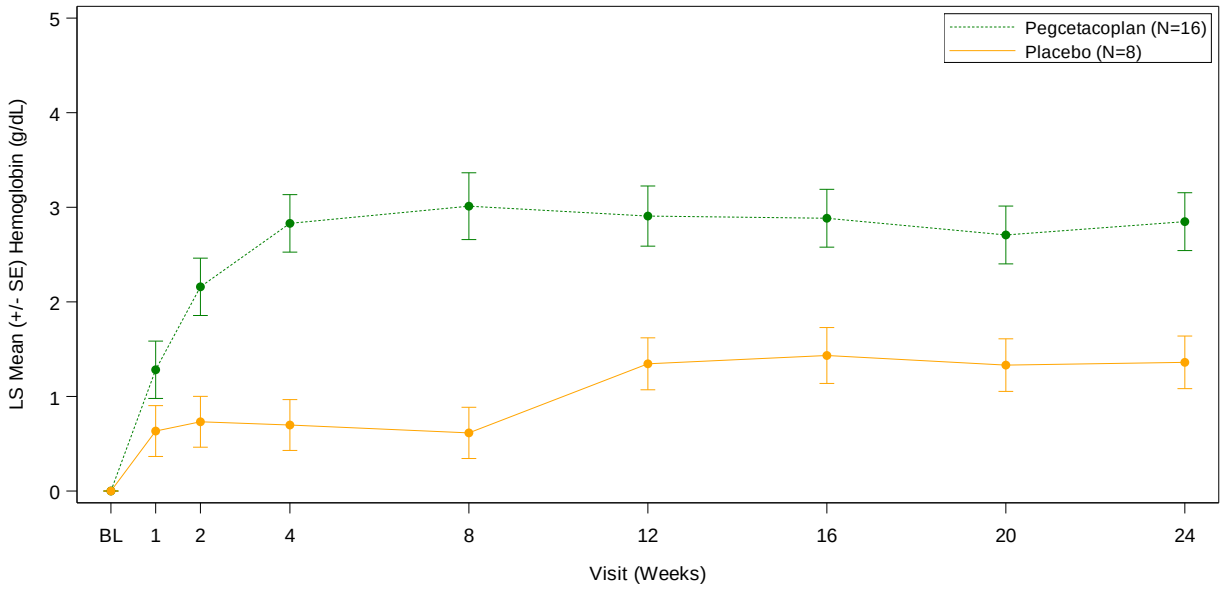
Source: Table 14.2.2.1.

[1] One patient who had assessment after first open-label extension dose was included in Part A for Week 24 visit.

Note: p-values were determined from a repeated measures mixed model comparing treatment groups. The model used treatment, strata (≥1/0 transfusions), visit, visit-by-treatment interaction, and Baseline assessment value as fixed effects.

CI=confidence interval; LS Mean=least square mean; Max=maximum; Min=minimum; SD=standard deviation; SE=standard error.

Figure 11-1. LS Mean (±SE) of Change from Baseline in Hemoglobin (g/dL) by Visit – ITT Set



Source: Figure 14.2.1.1; Listing 16.2.8.1.

BL=Baseline; ITT=intent-to-treat; LS Mean=least squares mean; SE=standard error.

A summary of Hb values in the ITT set including all assessments irrespective of ICEs is provided in Table 14.2.13.1.

11.1.2.1.1. Sub-group Analyses of Change from Baseline to Week 24 in Hemoglobin Level

11.1.2.1.1.1. Transfusion History

Table 14.2.2.2 provides a summary of Hb levels stratified by transfusion history and the corresponding changes from Baseline, in the absence of ICEs. The data after ICEs was set to missing.

Subgroup: ≥1 transfusion in prior 6 months

At Week 24, the mean (SD) change from Baseline in Hb was 3.5 g/dL (0.8) in the pegcetacoplan group (N=8) and 1.8 g/dL (2.0) in the placebo group (N=4). Baseline values were comparable for both arms.

Subgroup: No transfusions in prior 6 months

At Week 24, the mean (SD) change from Baseline in Hb was 2.2 g/dL (2.3) in the pegcetacoplan group, and 1.3 g/dL (0.5) in the placebo group. Baseline values were comparable for both arms.

No statistical comparison between groups could be done because the statistical model did not converge.

11.1.2.1.1.2. Rituximab History

A summary of Hb levels stratified by rituximab treatment history and the corresponding changes from Baseline in the absence of ICEs is provided in Table 14.2.2.3.

Subgroup: Previously treated with rituximab

The mean (SD) change from Baseline to Week 24 in Hb was higher in the pegcetacoplan group (N=7) at 3.8 g/dL (0.5), when compared with 1.8 g/dL (1.0) in the placebo group (N=7). No statistical comparison between groups could be done because the statistical model did not converge.

Subgroup: Rituximab-naïve

At Week 24, the mean (SD) change from Baseline in Hb was 2.2 g/dL (2.2) in the pegcetacoplan group (N=9) and 0.4 g/dL (not applicable [NA]) in the placebo group (N=1). The statistical comparisons could not be performed.

11.1.2.2. Transfusion Avoidance from Week 5 to Week 24 (Part A)

A summary of transfusion avoidance results from Week 5 to Week 24 set is provided in Table 11-3. Detailed information on the PRBC transfusions per patient is provided in Listing 16.4.14. At Week 24, there were no major differences in proportion of patients achieving transfusion avoidance in the pegcetacoplan group (12/16 patients [75.0%]) compared to the placebo group (5/8 patients [62.5%]), with a nominal p-value of 0.527.

Table 11-3. Summary of Transfusion Avoidance from Week 5 to Week 24 – ITT Set

Characteristic	Pegcetacoplan (N=16)	Placebo (N=8)
Week 24		
Number of Patients Achieving Transfusion Avoidance n (%)	12 (75.0%)	5 (62.5%)
Difference in Transfusion Avoidance Rate (95% CI)	0.125 (-0.257, 0.507)	
Odds Ratio (95% CI)	1.889 (0.182, 17.579)	
p-value	0.527	

Source: Table 14.2.3.1.

Notes:

Odds ratio, 95% CI, and p-value were generated using an exact CMH Test stratified on randomization strata of PRBC transfusion in prior 6 months.

The odds ratio was for odds of being a responder for pegcetacoplan versus placebo.

CI=confidence interval; CMH=Cochran-Mantel-Haenszel; PRBC=packed red blood cells.

11.1.2.2.1. Subgroup Analyses of Transfusion Avoidance from Week 5 to Week 24

11.1.2.2.1.1. Transfusion History

Table 14.2.3.2 provides a summary of transfusion avoidance, categorized by transfusion history in the ITT set.

Subgroup: ≥1 transfusion in prior 6 months

From Week 5 to Week 24, 5/8 patients (62.5%) patients treated with pegcetacoplan and 2/4 patients (50.0%) treated with placebo achieved transfusion avoidance.

Subgroup: No transfusions in prior 6 months

From Week 5 to Week 24, 7/8 patients (87.5%) treated with pegcetacoplan and 3/4 patients (75.0%) treated with placebo achieved transfusion avoidance.

11.1.2.2.1.2. Rituximab History

A summary of transfusion avoidance stratified by rituximab therapy is provided in Table 14.2.3.3.

Subgroup: Previously treated with rituximab

Four of 7 patients (57.1%) each in the pegcetacoplan and placebo groups achieved transfusion avoidance at Week 24.

Subgroup: Rituximab-naïve

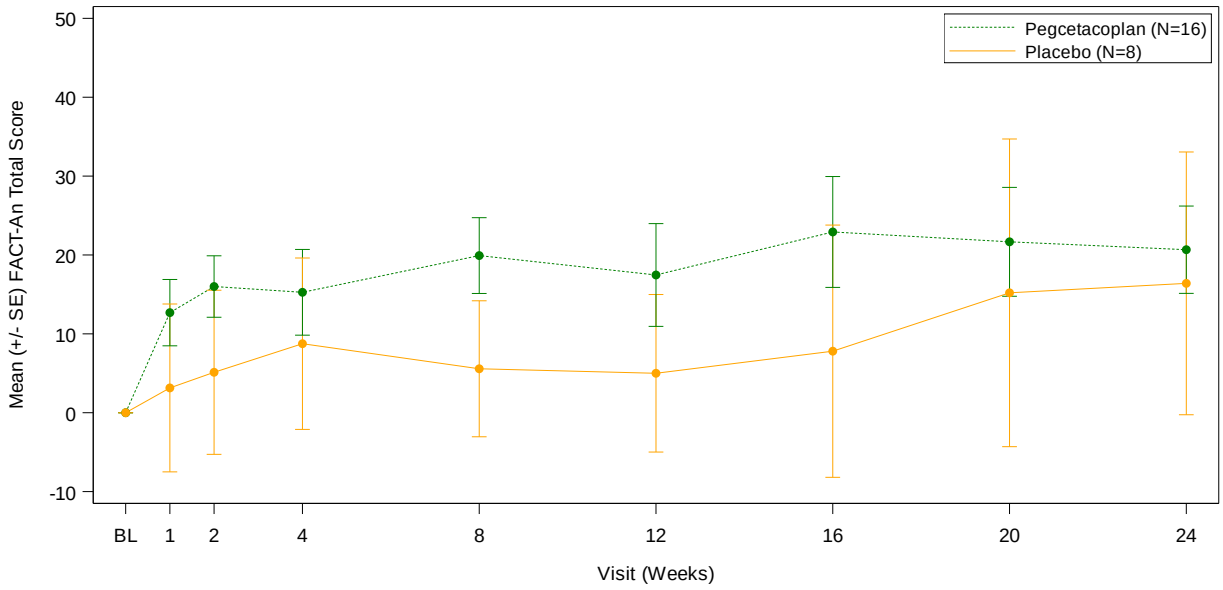
In this subgroup, 8/9 patients (88.9%) and 1/1 patient (100.0%) from the pegcetacoplan and placebo groups, respectively, achieved transfusion avoidance at Week 24.

11.1.2.3. Change from Baseline to Week 24 in the FACT-An Total Score (Part A)

Figure 11-2 illustrates the mean (±SE) change from Baseline in FACT-An total score by visit in the ITT set. Both treatment groups showed an improvement in total scores from Baseline through each visit up to Week 24. A slightly greater improvement in the total scores was observed in patients treated with pegcetacoplan when compared with those receiving placebo. Listing 16.4.11 presents the FACT-An scores by patient in the Safety set.

Table 14.2.4.1 summarizes the observed values and change from Baseline in FACT-An score, including total score and subscores - physical, social, emotional, and functional subscores, in the absence of ICEs, by visit. Overall, patients receiving pegcetacoplan showed a slightly higher improvement in the mean subscore changes at Week 24 than placebo, with the exception of the social and emotional subscores. No statistical comparisons of change from Baseline at Week 24 were made between the two groups due to model non-convergence.

Figure 11-2. Mean (±SE) Change from Baseline in FACT-An Total Score by Visit – ITT Set



Source: Figure 14.2.1.2.

BL=Baseline; FACT-An=Functional Assessment of Cancer Therapy-Anemia; ITT=intent-to-treat; SE=standard error.

Table 14.2.13.2 summarizes the change from Baseline in FACT-An scores including all assessments irrespective of ICEs in the ITT set.

11.1.2.3.1. Subgroup Analyses of Change from Baseline in FACT-An Total Score

11.1.2.3.1.1. Transfusion History

Table 14.2.4.2 presents a summary of change from Baseline in FACT-An score (total score and subscores) in the absence of ICEs, categorized by transfusion history.

Subgroup: ≥1 transfusion in prior 6 months

At Week 24, in this subgroup, the mean (SD) change in the FACT-An total score from Baseline was 28.0 (13.7) and 3.5 (60.1) in the pegcetacoplan and placebo groups, respectively. No statistical testing for the change from Baseline at Week 24 was made due to model non-convergence.

Subgroup: No transfusions in prior 6 months

At Week 24, the total scores improved in both groups as evidenced by the mean (SD) change from Baseline values of 15.4 (21.7) in the pegcetacoplan group and 25.0 (26.3) in the placebo group. No benefit was observed with pegcetacoplan. No statistical testing could be performed due to model non-convergence.

11.1.2.3.1.2. Rituximab History

A summary of change from Baseline in FACT-An score (total score and subscores) by rituximab therapy in the ITT set is provided in Table 14.2.4.3.

Subgroup: Previously treated with rituximab

The mean (SD) change in total scores from Baseline to Week 24 was nearly similar in both groups, 24.5 (13.0) with pegcetacoplan and 30.3 (23.9) with placebo. No statistical testing could be performed due to model non-convergence.

Subgroup: Rituximab-naïve

In this subgroup, the total scores improved from Baseline to Week 24, with a mean (SD) change from Baseline of 18.8 (22.2) in pegcetacoplan group. On the contrary, the mean total scores decreased from Baseline to Week 24, with a mean change from Baseline of -39.0 in placebo group. No statistical assessments were made due to model non-convergence.

11.1.3. Other Secondary Analyses

11.1.3.1. Secondary Efficacy Analyses – Part A

11.1.3.1.1. Number of PRBC transfusions from Week 5 to Week 24

The number of PRBC transfusions received by patients from Week 5 to Week 24 was summarized in Table 11-4; by-patient information on the number of PRBC transfusions is detailed in Listing 16.4.14. The mean (SD) number of PRBC transfusions received by the 16 patients who received pegcetacoplan was 1.5 (3.6), ranging from 0 to 13 PRBC transfusions. Eight patients from the placebo group had a mean (SD) of 1.1 (2.8), with a range of 0 to 8 PRBC transfusions.

Table 11-4. Number of PRBC Transfusions from Week 5 to Week 24

Parameter	Pegcetacoplan (N=16)	Placebo (N=8)
N	16	8
Mean (SD)	1.5 (3.62)	1.1 (2.80)
Median	0.0	0.0
Min, Max	0, 13	0, 8
Crude Rate	1.5	1.1
Crude Rate Ratio	1.30	
Wilcoxon Rank-Sum p-value	0.415	

Source: Table 14.2.5.1.

Notes:

The Wilcoxon Sign-Rank test was stratified using transfusion history (≥1/0).

Patients who withdrew from randomized treatment or received prohibited medication before Week 24 had their number of transfusions divided by the proportion of time from Week 5 to 24 completed.

Max=maximum; Min=minimum; SD=standard deviation.

11.1.3.1.2. Change from Baseline to Week 24 in LDH, Haptoglobin, Indirect Bilirubin, ARC, and D-dimer levels

Listing 16.2.8.2 provides by-patient results for all the serum chemistry laboratory parameters (except ARC) in the Safety set. By-patient test results for ARC are presented in Listing 16.2.8.1.

- Lactate Dehydrogenase

Table 14.2.6.1 provides a summary of LDH levels (U/L) by treatment group for different time points across the study, in the absence of ICEs. Figure 14.2.2.1 shows the mean (±SE) change from Baseline in LDH levels by visit.

Both pegcetacoplan and placebo groups exhibited a reduction in LDH levels from Baseline to Week 24, with a mean (SD) change from Baseline of -251.7 U/L (211.3) and -82.0 U/L (138.5), respectively. A greater reduction in LDH levels by Week 24 was noted with pegcetacoplan.

A summary of LDH (U/L) including all assessments irrespective of ICEs in the ITT set is provided in Table 14.2.13.3.

- Haptoglobin

Table 14.2.6.2 shows the haptoglobin levels (g/L) by treatment group in the absence of ICEs. Figure 14.2.2.2 provides a graphical representation of the mean (±SE) change from Baseline in haptoglobin levels by visit. The mean (SD) change from Baseline to Week 24 was 0.3 g/L (0.5) in the pegcetacoplan group and 0.01 g/L (0.02) in the placebo group. The statistical difference between groups was not determined because the mixed effects repeated measures model did not converge.

A summary of haptoglobin (g/L) including all assessments irrespective of ICEs in the ITT set is provided in Table 14.2.13.4.

- Indirect bilirubin

A summary of indirect bilirubin levels (µmol/L) by treatment group in the absence of ICEs is listed in Table 14.2.6.3. Figure 14.2.2.3 illustrates the mean (±SE) change from Baseline in indirect bilirubin levels by visit.

The pegcetacoplan group showed a decrease in the indirect bilirubin levels from Baseline to Week 24, by a mean (SD) change of -31.6 µmol/L (23.3). In the patients who received placebo, the indirect bilirubin levels slightly increased, with a mean (SD) change from Baseline to Week 24 of 8.2 µmol/L (19.3). The statistical difference between groups was not determined because the mixed effects repeated measures model did not converge.

A summary of indirect bilirubin (µmol/L) including all assessments irrespective of ICEs is provided in the ITT set in Table 14.2.13.5.

- Absolute Reticulocyte Count

Table 14.2.6.4 summarizes ARC (10^9/L) in the absence of ICEs. Mean (±SE) change from Baseline in ARC by visit is plotted in Figure 14.2.2.4.

The ARC levels decreased in both groups between Baseline and Week 24, with a mean (SD) changes from Baseline of -41.2 × 10^9/L (62.4) in the pegcetacoplan group and -38.0 × 10^9/L (19.9) in the placebo group. The LS Mean (SE) difference in change from Baseline between the two treatment groups was -20.7 × 10^9/L (16.0).

A summary of ARC (10^9/L) including all assessments irrespective of ICEs is provided in the ITT set in Table 14.2.13.6.

- D-dimer

A summary of D-dimer (µg/L FEU) by treatment group in the absence of ICEs in the ITT set is provided in Table 14.2.6.5. Figure 14.2.2.5 represents a mean (±SE) change from Baseline in D-dimer by visit in the ITT set.

At Baseline, the D-dimer levels were lower in the pegcetacoplan group (mean [SD]=1108.4 µg/L FEU [863.1]) as compared to the placebo group (mean [SD]=2531.8 µg/L FEU [3823.4]). At Week 24, the placebo group showed a greater reduction (improvement) in D-dimer levels, when compared with the pegcetacoplan group. The mean (SD) change from Baseline was -698.7 µg/L FEU (927.5) and -1722.8 µg/L FEU (3089.2) in the pegcetacoplan and placebo groups, respectively.

11.1.3.1.3. Normalization of Markers of Hemolysis (LDH, Indirect Bilirubin, and ARC) at Week 24

- LDH

Table 14.2.7.1 summarizes the proportion of patients with normalization of LDH at Week 24. A total of 13 patients in the pegcetacoplan group and 8 patients in the placebo group had abnormal LDH levels at Baseline. Five of 13 patients (38.5%) in the pegcetacoplan group and 1/8 patient (12.5%) in the placebo group achieved normalization in LDH levels at Week 24. The difference (95% CI) in normalization rate between the groups was 0.268 (-0.064, 0.601).

- Indirect Bilirubin

The proportion of patients with normalization of indirect bilirubin at Week 24 is summarized in Table 14.2.7.2. Of 13 patients in the pegcetacoplan group who had abnormal indirect bilirubin levels at Baseline, 9 patients (69.2%) achieved normalization at Week 24. Of 6 patients in the placebo group whose indirect bilirubin levels were abnormal at Baseline, 1 patient (16.7%) achieved normalization at Week 24. The difference (95% CI) in normalization rates between the two groups was 0.520 (0.131, 0.910).

- ARC

The proportion of patients with normalization of ARC at Week 24 is summarized in Table 14.2.7.3. At Baseline, 10 patients in the pegcetacoplan group and 8 patients in the placebo group had abnormal ARC levels. Of these, 4 patients (40.0%) treated with pegcetacoplan and 2 patients (25.0%) treated with placebo achieved normalization at Week 24. The difference (95% CI) in the normalization rate between the two groups was 0.114 (-0.290, 0.517).

- Haptoglobin

The proportion of patients with normalization of haptoglobin at Week 24 is summarized in Table 14.2.7.4. Of 15 patients who had abnormal haptoglobin results at Baseline in the pegcetacoplan group, 4 patients (26.7%) achieved normalization at Week 24. Of 6 patients with abnormal haptoglobin levels at Baseline in the placebo group, none achieved normalization at Week 24. The difference in the normalization rate (95% CI) between pegcetacoplan and placebo was 0.274 (0.049, 0.499), suggesting a meaningful difference between the two groups.

11.1.3.1.4. Time to First Normalization from Baseline to Week 24 – Hb, LDH, Indirect Bilirubin, and ARC

- Hemoglobin

Time to Hb normalization over the initial 24 weeks of the study is summarized in Table 14.2.8.2 and graphically shown in Figure 14.2.2.7. Seven of 16 patients (43.8%) in the pegcetacoplan group achieved Hb normalization during the initial 24 weeks of the study. Furthermore, 25% of the patients in this group reached their first normalization by 8.1 weeks. In contrast, none of the 8 patients in the placebo group achieved Hb normalization.

- LDH

Figure 14.2.2.6 shows the time from Baseline to normalization of LDH levels during Part A. Six of 13 patients (46.2%) in the pegcetacoplan group and 2/8 patients (25.0%) in the placebo group achieved normalization during the initial 24 weeks of the study.

- Indirect Bilirubin

Time from Baseline to normalization of indirect bilirubin levels during Part A is illustrated in Figure 14.2.2.8. The evaluation should be carefully considered as the number of pegcetacoplan-treated patients potentially reaching normalization is low from Week 8 onwards. Eleven out of 13 patients (84.6%) in the pegcetacoplan group and 1/6 patient (17.6%) in the placebo group reached normalization within 24 weeks of participating in this study. The median time to normalization from Baseline with pegcetacoplan was 1.1 weeks. Nine of 13 patients (69.2%) in the pegcetacoplan group and 1/6 patient (16.7%) in the placebo group had their indirect bilirubin levels normalized within the first 4 weeks of starting treatment.

- ARC

Figure 14.2.2.9 presents time from Baseline to normalization in ARC levels during Part A. The evaluation should be carefully considered as the number of pegcetacoplan-treated patients potentially reaching normalization is low from Week 8 onwards. There were 9/10 patients (90.0%) treated with pegcetacoplan and 3/8 patients (37.5%) treated with placebo, who got normalized by Week 24. The median time to normalization was 4 weeks with pegcetacoplan, while the median time to normalization was not reached in the placebo group.

- Time to First Normalization From Baseline to Week 24 for Haptoglobin Level

Table 14.2.8.1 shows the time to haptoglobin normalization during the initial 24 weeks of the study. Time from Baseline to normalization in haptoglobin levels during Part A is depicted in Figure 14.2.2.10. In the pegcetacoplan group, haptoglobin normalization was observed in 7/15 patients (46.7%) during the initial 24 weeks. None of the 6 patients in the placebo group had normalization in haptoglobin levels by Week 24.

11.1.3.1.5. Number of PRBC Units Transfused from Week 5 to Week 24

The number of PRBC units transfused from Week 5 to Week 24 by treatment group is presented in Table 14.2.9.1. The PRBC transfusions by-patient is provided in Listing 16.4.14.

The mean (SD) number of PRBC units transfused during this period was 2.5 (6.0) in the pegcetacoplan group and 1.9 (4.6) in the placebo group. The number of PRBC units transfused ranged from 0 to 19.1 in patients treated with pegcetacoplan and 0 to 13 in placebo-treated patients.

11.1.3.1.6. Change from Baseline to Week 24 in the FACIT-F Subscale, SF-12, and EQ-5D-5L Scores

- FACIT-F Subscale Score of the FACT-An Scale

Table 14.2.10.3 summarizes the FACIT-F subscale score of the FACT-An Scale in the absence of ICEs. The Week 24 assessments were completed in 12/16 patients (75.0%) treated with pegcetacoplan and 5/8 patients (62.5%) treated with placebo . At Week 24, both the pegcetacoplan and placebo groups showed an improvement in fatigue from Baseline, with a mean (SD) change from Baseline in the FACIT-F scores of 9.7 (11.0) and 8.8 (18.1), respectively. Pegcetacoplan group demonstrated a higher percentage of patients (50.0% [8/16 patients]) achieving a ≥4-point improvement from Baseline compared with the placebo group (37.5% [3/8 patients]).

- SF-12

A summary of SF-12 in the absence of ICEs is provided in Table 14.2.10.1. By-patient details on the SF-12 health survey results in the Safety set are presented in Listing 16.4.8. The SF-12 assessment evaluates physical and mental component scores (PCS and MCS). Eleven of 16 randomized patients (68.75%) in the pegcetacoplan group and 5/8 randomized patients (62.5%) in the placebo group had SF-12 assessments at Week 24. The change from Baseline to Week 24 in PCS was similar in both groups, with a mean (SD) increase of 5.0 (8.0) with pegcetacoplan and 4.5 (11.9) with placebo. An increase in the MCS from Baseline to Week 24 was noted in both treatment groups, with a mean (SD) change of 5.5 (9.9) with pegcetacoplan and 2.5 (9.8) with placebo.

- EQ-5D-5L

The EQ-5D-5L scores in the absence of ICEs are summarized in Table 14.2.10.2; by-patient results of this questionnaire for the Safety set are available in Listing 16.4.10. The results revealed a slight improvement in mobility, usual activities, pain/discomfort, anxiety/depression with pegcetacoplan, while a slight improvement in self-care was displayed with placebo. At Week 24, the patients reported a greater improvement in their overall health on the day of the questionnaire, with pegcetacoplan showing a mean (SD) change from Baseline of 17.7 (17.0), compared with a mean (SD) change of 4.8 (26.6) with placebo.

A summary of change from Baseline in SF-12, EQ-5D-5L, and FACIT-F including all assessments irrespective of ICEs is provided in Tables 14.2.13.7, 14.2.13.8, and 14.2.13.9, respectively.

11.1.3.2. Secondary Efficacy Analyses– Part B

11.1.3.2.1. Change from Baseline to Week 48 in Hb, LDH, Haptoglobin, Indirect Bilirubin, ARC, and D-dimer Levels

The summaries of these parameters are tabulated in in Table 14.2.2.1 (hemoglobin), Table 14.2.6.1 (LDH), Table 14.2.6.2 (haptoglobin), Table 14.2.6.3 (indirect bilirubin), Table 14.2.6.4 (ARC), and Table 14.2.6.5 (D-dimer). The mean (SD) changes from Baseline for Hb and haptoglobin were comparable or slightly higher in the switching group (patients who were on placebo in Part A and started open-label pegcetacoplan treatment in Part B) with mean (SD) values of 3.4 g/dL (1.0) and 0.7 g/L (0.3), respectively, in the switching group and 3.0 g/dL (2.1) and 0.2 g/L (0.2), respectively, in the pegcetacoplan-throughout group (Table 14.2.2.1, Table 14.2.6.2). The D-dimer and LDH levels decreased more over 48 weeks in the switching group (mean [SD] of -3595.0 µg/L FEU

[4879.0] and -259.3 U/L [52.3], respectively) than in the pegcetacoplan-throughout group (mean [SD] of -596.6 µg/L FEU [938.0] and -220.3 U/L [168.3], respectively), suggesting that placebo-treated patients tend to experience the same effects that pegcetacoplan-treated patients upon treatment start (Table 14.2.6.5, Table 14.2.6.1). Pegcetacoplan-throughout group showed a comparable or slightly higher reduction of indirect bilirubin levels compared with placebo (mean [SD] of -40.2 µmol/L [28.5] and -33.4 µmol/L [25.2], respectively) (Table 14.2.6.3). Additionally, the ARC levels decreased less in the pegcetacoplan-throughout group (-39.6 × 10^9/L [56.0]) than in the switching group (-118.2 × 10^9/L [73.1]) (Table 14.2.6.4).

11.1.3.2.2. Normalization of Markers of Hemolysis (LDH, Indirect Bilirubin, and ARC) at Week 48

Due to the early termination of the study, the scope of analysis for this study was changed. As a result, normalization of hemolysis markers (LDH, indirect bilirubin, and ARC) at Week 48 (or beyond Week 24) was not evaluated. Hence, no statistical results were generated for this endpoint analysis.

11.1.3.2.3. Durability of Response in Pegcetacoplan Patients Who Achieved Primary Endpoint at Week 24

Due to the termination of the study, the durability of response was not analyzed.

11.1.3.2.4. Change from Baseline to Week 48 in FACT-An Score, FACIT-F Subscale Score of FACT-An Scale, SF-12 Score, and EQ-5D-5L Score

- FACT-An Score

Table 14.2.4.1 summarizes the FACT-An total score and subscores for each component (physical, social, emotional, and functional wellbeing) by treatment group for each part of the study. Ten/16 patients (62.5%) randomized to pegcetacoplan had FACT-An total scores assessed at Week 48. The mean (SD) FACT-An total score at Baseline was 102.0 (23.0), which improved to 131.2 (15.5) at Week 48, with a mean (SD) change from Baseline of 29.2 (19.1) for those randomized to pegcetacoplan in Part A who continued treatment in Part B. The mean (SD) FACT-An total score change from Baseline was 39.5 (29.8) for patients randomized to placebo in Part A who started open-label pegcetacoplan in Part B (4/8 patients [50.0%]).

- FACIT-F Subscale Score of FACT-An Scale

The FACIT-F summary in the absence of ICEs is provided in Table 14.2.10.3. The FACIT-F scores increased from Baseline (mean [SD]=30.2 [12.0]) to Week 48 (mean [SD]=42.0 [7.8]), with a change from Baseline of 11.8 (11.3) for those patients randomized to pegcetacoplan in Part A (10/16 patients [62.5%]). Similarly, for the patients randomized to placebo in Part A and then treated with open-label pegcetacoplan in Part B (4/8 patients [50.0%]) showed an increased mean (SD) value from Baseline (20.5 [16.3] to Week 48 (42.3 [9.7]), with a change from Baseline of 21.75 (14.3), thereby suggesting an improvement in responses after treatment with pegcetacoplan. Seven of 10 patients (70.0%) in the pegcetacoplan group and 3/4 patients (75.0%) in the placebo group during Part A, who were evaluated for change in FACIT-F scores at Week 48, reported having ≥4-point improvement from Baseline.

- SF-12

A summary of SF-12 survey in the absence of ICEs is tabulated in Table 14.2.10.1. Ten of 16 randomized patients (62.5%) from the pegcetacoplan group and 4/8 (50.0%) were evaluated for SF-12 scores at Week 48. The PCS improved by a mean (SD) change of 7.7 (8.3) from Baseline (mean [SD]=37.4 [8.6]) to Week 48 (mean [SD]=45.1 [9.4]) in the pegcetacoplan group. The PCS improved by a mean (SD) change of 14.5 (9.2) from Baseline (mean [SD]=31.7 [8.8]) to Week 48 (mean [SD]=46.2 [5.5]) in the placebo group. A similar pattern noted in MCS, which increased from Baseline (mean [SD]=51.9 [12.3]) to Week 48 (55.9 [8.2]) by a mean (SD) change of 3.9 (12.5) in the pegcetacoplan group and from Baseline (mean [SD]=44.8 [14.2]) to Week 48 (48.9 [8.4]) by a mean (SD) change of 4.1 (8.6) in the placebo group.

- EQ-5D-5L

Table 14.2.10.2 summarizes EQ-5D-5L scores in the absence of ICEs. A marginal increase in the scores (for mobility, self-care, usual activities, pain/discomfort, anxiety/depression, was noted from Baseline to Week 48 in both pegcetacoplan and placebo groups. A notable improvement in the rating given by the patients for their overall health on the day of questionnaire at Week 48 was noted, by a mean (SD) change from Baseline of 18.2 (20.6) in the pegcetacoplan group and 17.5 (16.6) in the placebo group.

11.1.4. Tertiary Efficacy – Part C

Due to the early termination of the study, Week 96 assessments could not be performed. The last available evaluations during the treatment period before terminating the study were performed at Week 88.

11.1.4.1. Change from Baseline to Week 96 in Hb, LDH, Haptoglobin, Indirect Bilirubin, ARC, D-dimer Levels

No Week 96 assessments were performed due to premature study termination.

11.1.4.2. Normalization of Markers of Hemolysis (LDH, Indirect Bilirubin, ARC Levels) at Week 96

The normalization of hemolysis markers (LDH, indirect bilirubin, and ARC) beyond Week 24 was not assessed. Furthermore, due to the early termination, no patients reached Week 96 time point. Therefore, this endpoint was not analyzed.

11.1.4.3. Change from Baseline to Week 96 in FACT-An Score, FACIT-F Subscale Score of FACT-An Scale, SF-12 Score, and EQ-5D-5L Score

The change from Baseline in FACT-An, FACIT-F, SF-12, and EQ-5D-5L scores at Week 96 was not evaluated due to premature termination of the study.

11.2. Statistical/Analytical Issues

The statistical methods used for the analyses of study results are detailed in the SAP, version 2.0, dated 22 October 2024 (Appendix 16.1.9).

11.2.1. Adjustments for Covariates

To preserve the Type 1 error, a fixed-sequence testing strategy was used; hence, statistical significance with the first key secondary endpoint was only concluded if statistical significance was achieved with the analysis of the primary endpoint.

The MMRM with the fixed effects of treatment, strata, visit, visit-by-treatment interaction, and Hb level at Baseline was selected as covariate using an unstructured covariance matrix (when it failed, an auto-regressive, and then a compound symmetry model was to be used) and the Kenward-Roger method for calculating the degrees of freedom, for the analysis of:

Key secondary efficacy endpoints of

- Change from Baseline to Week 24 in Hb level
- Change from Baseline to Week 24 in the FACT-An score

Other secondary efficacy endpoints of

- Change from Baseline at Week 24 in LDH, haptoglobin, indirect bilirubin, ARC, and D-dimer
- Change from Baseline at Week 24 in SF-12, EQ-5D-5L, and the FACIT-F subscale score of the FACT-An scale

11.2.2. Handling of Dropouts or Missing Data

In general, missing values were not to be imputed for the analysis unless otherwise stated in the SAP. Missing dates were not to be imputed. However, if there was a missing start date for an AE, the AE was to be considered as treatment-emergent. For concomitant medications, any medication was to be regarded as concomitant if the start date was missing. In the case of missing end dates for AEs and concomitant medications, the events and medications were to be considered as ongoing at the study end or end of Parts A, B, and C.

11.2.3. Interim Analyses and Data Monitoring

No interim statistical analyses were performed.

11.2.4. Multiple Comparisons/Multiplicity

The hierarchical testing was applied to the primary and key secondary efficacy endpoint analyses, no further multiplicity control was applied.

11.2.5. Use of an Efficacy Subset of Patients

Not applicable.

11.2.6. Examination of Subgroups

Subgroup analyses were conducted on the primary and key secondary endpoints for the following:

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

Further details on the statistical methods used are presented in Section 9.7.3, and the results of these subgroup analyses are presented in Section 11.1.1 and Section 11.1.2.

11.2.7. Tabulation of Individual Response Data

Individual efficacy tabulated data can be found in Appendix 16.2.6.

11.3. PK and PD Analyses Results

The PK and PD analyses were categorized as exploratory analyses for this study.

Note: During the study, two biological samples (each from Patients 440103 and 390402) were delivered to the central laboratory in a refrigerated condition instead of being frozen, as required for ADA, PK, and PD (cytokines and complement markers). These samples were subsequently frozen at the central laboratory before being sent to the bioanalytical laboratory for their respective analyses. Patient 390402 was a screen failure. Further details regarding this process deviation in Patient 440103 are provided in the NTF included in the Appendix 16.19.

11.3.1. PK Analysis

11.3.1.1. Pegcetacoplan PK Concentrations at Week 24 and Week 48

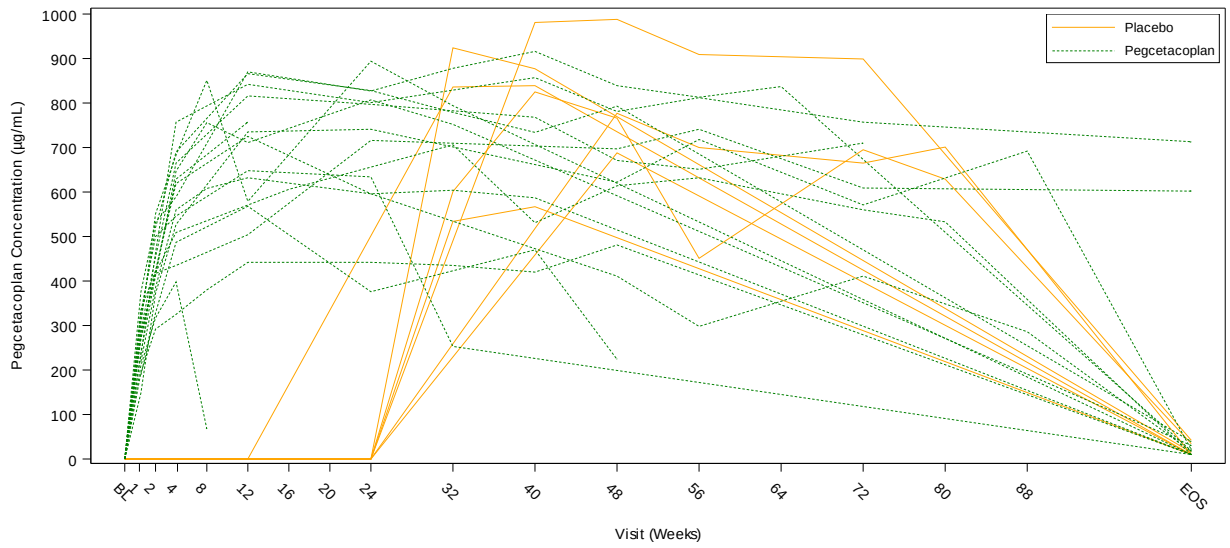
A summary of individual pegcetacoplan trough concentrations (µg/mL) in the PK set for all time points are provided in Table 14.2.11.1. By-patient listings of individual serum concentrations are provided in Listing 16.2.5.2. Individual pegcetacoplan trough concentrations on a linear scale are presented in the Figure 11-3 and on a semi-log scale in Figure 14.3.1.4.

At Week 24, trough concentrations were measured in 13/16 patients (81.25%) treated with pegcetacoplan in Part A. The patients receiving pegcetacoplan had measurable drug concentrations at Week 24, with a mean (SD) concentration of 696.5 µg/mL (158.3), ranging from 376 µg/mL to 894 µg/mL.

At Week 48, trough concentrations were measured in 10/16 patients (62.5%) treated with pegcetacoplan and in 4/8 patients (50.0%) treated with placebo in Part A (who eventually switched to open-label pegcetacoplan treatment during Part B). At Week 48, all patients were on open-label pegcetacoplan treatment. The mean (SD) pegcetacoplan concentration was 613.3 µg/mL (192.0) in the pegcetacoplan-treated patients, with concentrations ranging from 224 µg/mL to 839 µg/mL. In the placebo-pegcetacoplan group, the mean (SD) concentration was 804.8 µg/mL (128.4) and ranged from 688 µg/mL to a maximum of 988 µg/mL. A decrease in the mean concentration was observed at Week 48 (end of Part B) when compared to Week 24 (end of Part A) for the group of patients treated with pegcetacoplan in Part A. At EOS, it was noted that Patients 340101 and 440301 had unusually high serum concentrations (713 and 710 µg/mL, respectively) compared to all other patients which had concentrations close to the lower limit of quantification. This can be explained by the fact that the EOT visit occurred on the last dosing day for Patient 340101, and Patient 440301 was receiving pegcetacoplan outside the study setting as detailed in the Listing 16.4.3.

Figures 14.3.1.5 and 14.3.1.6 display the median pegcetacoplan trough serum concentrations on a linear scale and semi-log scale, respectively.

Figure 11-3. Individual Pegcetacoplan Trough Serum Concentrations – Linear Scale – PK Set



Source: Figure 14.3.1.1.

Notes:

Open-label treatment began at Week 24.

The EOS visit followed end of treatment/early termination and could occur at any time after Baseline.

Concentrations below the lower limit of quantification (10.0 µg/mL) were replaced with 0 µg/mL prior to the start of treatment with pegcetacoplan and with 10 µg/mL after the start of treatment with pegcetacoplan.

There was a patient initially assigned to placebo for whom pegcetacoplan trough serum concentrations appeared to start increasing from Week 12. This was due to a missing Week 24 sample.

BL=Baseline; EOS=End of study.

11.3.2. Pharmacodynamic Analyses

11.3.2.1. Changes from Baseline to Week 24 and Week 48 in Complement Biomarkers

Table 14.2.12.1 summarizes the complement biomarker PD results. At Week 24, the changes from Baseline in complement biomarkers were evaluated in 13/16 patients (81.3%) in the pegcetacoplan group and 7/8 patients (87.5%) in the placebo group. Similarly, at Week 48, the changes from Baseline in complement biomarkers were assessed in 10/16 patients (62.5%) patients initially treated with pegcetacoplan and 4/8 patients (50.0%) in the placebo group switched to pegcetacoplan after Week 24. By-patient listings of complement biomarkers in the PD set is provided in Listing 16.3.1. Figure 14.3.1.7 shows individual complement biomarker PD parameters during the study. Median complement biomarker PD parameters during the study are plotted in Figure 14.3.1.8.

- Complement C3 Levels (mg/dL)

The observed mean (SD) values for the complement C3 levels at Baseline was 63.6 mg/dL (12.3) in the pegcetacoplan group and 77.2 mg/dL (20.8) in the placebo group. At Week 24, the pegcetacoplan group showed an increase in the complement C3 levels (mean [SD]=143.9 mg/dL [13.0]) compared to Baseline, with a mean (SD) change from Baseline of 80.9 mg/dL (15.5). The placebo group exhibited little to no change in C3 levels at Week 24 (75.4 mg/dL [16.2]), with a mean (SD) change from Baseline of -1.74 mg/dL [19.5]). The complement C3 levels increased from Baseline (mean [SD]=66.3 mg/dL [9.0]) to Week 48 (mean [SD]=144.1 mg/dL [15.0]), with a mean (SD) change from Baseline of 81.7 mg/dL (15.2) close to those already observed at Week 24 for the patients initially on pegcetacoplan. For the patients initially on placebo switching to pegcetacoplan after Week 24, a similar pattern of increase in the C3 levels from Baseline (mean [SD]=84.9 mg/dL [22.0]) to Week 48 (mean [SD]=155.3 mg/dL [8.4]) was observed, with a mean (SD) change from Baseline of 70.4 mg/dL (20.3) (as compared to no change at Week 24) (Table 14.2.12.1).

- Functional Assays for Classical Complement Pathway activity (CH50 in U/mL)

The activity of classical complement pathway, measured by CH50 (U/mL) was assessed in both treatment groups. The observed mean (SD) CH50 at Baseline was 33.8 U/mL (30.8) and 49.9 U/mL (39.6) in the pegcetacoplan and placebo groups, respectively. At Week 24, the mean (SD) CH50 was 29.8 U/mL (28.5), with a mean (SD) change from Baseline of -4.9 U/mL (21.9), while in the placebo-treated patients, the mean (SD) CH50 at Week 24 was 39.3 U/mL (30.9), with a mean (SD) change from Baseline of -10.6 U/mL (15.5). The mean (SD) change from Baseline (mean [SD]=35.9 U/mL [30.5]) to Week 48 (mean [SD]=33.9 U/mL [38.9]) in CH50 was -7.1 U/mL (21.5) in patients treated with pegcetacoplan in Part A. In patients treated with placebo in Part A and switched to pegcetacoplan after Week 24, the mean (SD) change from Baseline (mean [SD]=42.3 U/mL [42.6]) to Week 48 (mean [SD]=28.0 U/mL [34.3]) in CH50 was -14.3 U/mL (11.2) (Table 14.2.12.1).

- Functional Assays for Alternative Complement Pathway activity (AH50, in U/mL)

The alternative complement pathway activity, measured by AH50 (U/mL) was assessed in both treatment groups. In the pegcetacoplan-treated patients, the AH50 decreased from Baseline (mean [SD]=115.7 U/mL [19.9]) to Week 24 (mean [SD]=70.8 U/mL [61.3]), with a mean (SD) change from Baseline of -49.4 U/mL (52.2), indicating a reduction of the alternative complement pathway activity. Similarly, patients treated with placebo showed a decrease in AH50 at Week 24 (mean [SD]=123.3 U/mL [20.6]) when compared to Baseline (mean [SD]=135.9 U/mL [23.7]), with a mean (SD) change of -12.6 U/mL (31.5). After 48 weeks of treatment, patients showed a decreased AH50 from Baseline (mean [SD]=114.1 [18.3]) to Week 48 (mean [SD]=76.9 U/mL [51.3]), reflecting a mean (SD) change of -45.4 U/mL (41.0) in the pegcetacoplan group, while the mean [SD] change from Baseline (mean [SD]=141.0 U/mL [26.9]) to Week 48 (mean [SD]=65.3 U/mL [43.0]) was -75.8 U/mL (34.1) in the patients who were initially on placebo (in Part A) and switched to pegcetacoplan after Week 24 (Table 14.2.12.1).

Overall, pegcetacoplan showed a consistent effect on the complement C3 levels as well as classical and alternative complement pathway activity. The results (change from Baseline) at Weeks 24 and 48 were comparable. No statistical testing for the two treatment groups could be performed due to model non-convergence.

11.3.2.2. Changes from Baseline Through Week 24 and Week 48 in C3 Deposition on RBCs by Flow Cytometry

Table 14.2.12.1 provides a summary of the actual values and change from Baseline in C3 deposition on RBCs by Flow Cytometry.

At Week 24, 13/16 patients (81.25%) treated with pegcetacoplan and 7/8 patients (87.5%) treated with placebo were assessed for the proportion (%) of RBCs with C3d deposition. In the pegcetacoplan group, the proportion of RBCs with C3d deposition decreased with a mean (SD) change from Baseline of -5.8% (37.4), while the proportion increased by a mean (SD) change of 8.8% (24.3) with placebo. Median (min – max) percent change from Baseline was -45.7% (-99.2, 638.0) in the pegcetacoplan-treated patients as compared to 39.4% (-47.2, 217.3) in the placebo-treated patients.

At Week 48, 9/16 patients (56.25%) initially treated with pegcetacoplan in Part A exhibited an increase in the proportion of RBCs with C3d deposition from Baseline, with a mean (SD) change of 3.3% (36.9) and a small change of 0.1% (19.0) in patients who received placebo in Part A and switched to pegcetacoplan after Week 24. Median (min – max) percent change from Baseline was 22.2% (-67.7, 573.1%) in the pegcetacoplan-treated patients throughout the study as compared to 21.6% (-61.0, 42.4) in the placebo-treated patients switching to pegcetacoplan in Part B.

Overall, the effect of pegcetacoplan on the proportion of RBCs with C3d deposition displayed an inconsistent pattern, with an apparent decrease in C3d deposition on RBCs observed initially through Week 24 probably driven by one or a few patients with high increase despite a decreasing trend in most patients (median decrease by about 46%), followed by an apparent increase in RBCs with C3d deposition at Week 48 again probably driven by one or few patients with very high increases. Given the low sample size and the high variability (SD values higher than the mean change), interpretation is unclear. The evolution of the proportion of RBCs with C3d deposition during Part B was also affected by the same issues related to high variability and an even smaller sample size, thus also precluding firm conclusions.

11.3.2.3. Changes from Baseline to Week 24 and Week 48 in Inflammatory Biomarkers

Pro-inflammatory cytokines summaries are tabulated in Table 14.2.12.2. By-patient listing of inflammatory biomarkers is provided in Listing 16.3.2. Individual and median pro-inflammatory cytokine parameters during the study are plotted in Figures 14.3.1.9 and 14.3.1.10, respectively. The results were comparable between the two treatment groups at Week 24. No clear changes were observed in TNFα, IL-6, IL-10, IFNγ, and IL-1β at Weeks 24 and 48.

11.4. Efficacy Conclusions

11.4.1. Summary of Efficacy Results

Primary endpoint

The study's primary endpoint was not met. At Week 24, 8/16 patients (50.0%) treated with pegcetacoplan achieved a response, compared with 2/8 patients (25.0%) treated with placebo. No statistically significant difference was observed in the response rates between the two groups

(p-value=0.262). Failure to meet the primary endpoint might have been related to the premature discontinuation of the study, leading to an insufficient sample size.

Key secondary endpoints

Because the primary endpoint was not met, formal statistical testing was not allowed for the key secondary endpoints.

- The mean (SD) change from Baseline to Week 24 was 2.8 g/dL (1.9) in the pegcetacoplan group and 1.5 g/dL (1.1) in the placebo group. The difference in the LS Mean change from Baseline between the two treatment groups was 1.5 g/dL (95% CI=0.65, 2.33), thereby suggesting an improvement in Hb levels from Baseline to Week 24 in the pegcetacoplan group compared with placebo.
- At Week 24, there were no major differences in proportion of patients achieving transfusion avoidance in the pegcetacoplan group (12/16 patients [75.0%]) compared to the placebo group (5/8 patients [62.5%]).
- Patients receiving pegcetacoplan showed slightly greater improvement in the FACT-An total scores at Week 24. The mean subscores for physical and functional components improved by Week 24, with a slightly higher mean (SD) change reported with pegcetacoplan than placebo.

Other secondary endpoints

- Seven of 16 patients (43.8%) in the pegcetacoplan group achieved Hb normalization and none of the 8 patients in the placebo group achieved Hb normalization during the first 24 weeks of the study.
- The mean (SD) number of PRBC units transfused from Week 5 to Week 24 was 1.5 (3.6) in the pegcetacoplan group and 1.1 (2.8) in the placebo group.
- Both pegcetacoplan and placebo groups exhibited a reduction in LDH levels from Baseline to Week 24, with a mean (SD) change from Baseline of -251.7 U/L (211.3) and -82.0 U/L (138.5), respectively. A greater reduction in LDH levels by Week 24 was noted with pegcetacoplan. Five of 13 patients (38.5%) in the pegcetacoplan group and 1/8 patient (12.5%) in the placebo group achieved normalization in LDH levels at Week 24. The difference (95% CI) in normalization rate between the groups was 0.268 (-0.064, 0.601).
- The mean (SD) change in haptoglobin concentrations from Baseline to Week 24 was 0.3 g/L (0.5) in the pegcetacoplan group and 0.01 g/L (0.02) in the placebo group. In addition, 4/15 patients (26.7%) who had abnormal haptoglobin results at Baseline in the pegcetacoplan group achieved normalization at Week 24 as compared to 0/6 on placebo. The difference in the normalization rate (95% CI) between pegcetacoplan and placebo was 0.274 (0.049, 0.499), suggesting a meaningful difference between the two groups.
- The pegcetacoplan group showed a decrease in the indirect bilirubin levels from Baseline to Week 24, by a mean (SD) change of -31.6 µmol/L (23.3). In the patients who received placebo, the indirect bilirubin levels slightly increased, with a mean (SD) change from Baseline to Week 24 of 8.2 µmol/L (19.3). In addition, of 13 patients in the pegcetacoplan group who had abnormal indirect bilirubin levels at Baseline, 9 patients (69.2%) achieved normalization at Week 24. Of 6 patients in the placebo group whose indirect bilirubin levels were abnormal at Baseline, 1 patient (16.7%) achieved normalization at Week 24. The difference (95% CI) in normalization rates between the two groups was 0.520 (0.131, 0.910).

- The ARC levels decreased in both groups between Baseline and Week 24, with mean(SD) changes from Baseline of -41.2 × 10^9/L (62.4) in the pegcetacoplan group and -38.0 × 10^9/L (19.9) in the placebo group. The LS Mean (SE) difference in change from Baseline between the two treatment groups was -20.7 × 10^9/L (16.0). At Baseline, 10 patients in the pegcetacoplan group and 8 patients in the placebo group had abnormal ARC levels. Of these, 4 patients (40.0%) treated with pegcetacoplan and 2 patients (25.0%) treated with placebo achieved normalization at Week 24. The difference (95% CI) in the normalization rate between the two groups was 0.114 (-0.290, 0.517).
- At Baseline, the D-dimer levels were lower in the pegcetacoplan group (mean [SD]=1108.4 µg/L FEU [863.1]) as compared to the placebo group (mean [SD]=2531.8 µg/L FEU [3823.4]). At Week 24, the placebo group showed a greater reduction (improvement) in D-dimer levels, when compared with the pegcetacoplan group. The mean (SD) change from Baseline was -698.7 µg/L FEU (927.5) and -1722.8 µg/L FEU (3089.2) in the pegcetacoplan and placebo groups, respectively
- The mean changes from Baseline to Week 24 in the FACIT-F subscale, SF-12, and EQ-5D-5L scores demonstrated a minimal change from Baseline, consistent with better improvement in pegcetacoplan group in all measures, except EQ-5D-5L self-care (no change from Baseline).

Week 48 endpoints

- By Week 48, the majority of patients had discontinued from the study; hence, it was not possible to meaningfully evaluate the efficacy results at Week 48.

Pharmacokinetics and Pharmacodynamics

- At Weeks 24 and 48, the serum pegcetacoplan trough concentrations were measurable, with mean (SD) values of 696.5 (158.35) µg/mL and 613.3 (192.0) µg/mL, respectively for those treated with pegcetacoplan in Part A. All patients receiving pegcetacoplan showed measurable drug concentrations from Week 1 to EOT/ET visits. Overall, pegcetacoplan trough concentrations were in-line with observations from previous studies in which the same dosing regimen was applied (Pegcetacoplan-APL-2-IB 2023).
- The mean complement C3 levels increased from Baseline to Weeks 24 and 48, with patients receiving pegcetacoplan showing a greater increase compared to placebo.
- Patients treated with pegcetacoplan in Part A showed a decrease in AH50 (alternative complement pathway activity) when compared to placebo. Overall, pegcetacoplan showed a consistent effect in complement C3 levels as well as alternative complement pathway activity. No statistical comparisons between the two treatment groups were made.
- The effect of pegcetacoplan on the proportion of RBCs with C3d deposition displayed an inconsistent pattern, with an apparent decrease in C3d deposition on RBCs observed initially through Week 24, followed by an apparent increase in RBCs with C3d deposition by Week 48. A small, yet consistent increase was observed in the placebo switching to pegcetacoplan group. The presence of some patients with extreme changes from baseline and the high variability of the results in the presence of a small sample size preclude any conclusion.
- No clear changes from Baseline were observed in TNFα, IL-6, IL-10, IFNγ, and IL-1β at Weeks 24 and 48 and in any of the treatment groups.

11.4.2. Conclusions

The primary efficacy endpoint of response to treatment at Week 24 was not met. Comparison of the change from Baseline to Week 24 in Hb and other parameters (haptoglobin, indirect bilirubin, LDH) between the active and the placebo group suggests that pegcetacoplan improved anemia in this population considering that the patients had severe CAD related anemia at entry (Baseline Hb value of <9.0 g/dL).

12. SAFETY EVALUATION

All safety analyses were performed on the Safety set, which included all patients who received at least one dose of IMP. The patients were analyzed according to the treatment they received.

12.1. Extent of Exposure

Table 12-1 summarizes the study treatment exposure. A summary of the treatment duration, total drug administered, and infusion completion and interruption rates across different parts of the study, comparing pegcetacoplan and placebo treatment groups, is presented in Table 14.1.7. The IMP administration schedules were presented by patient in Listings 16.2.5.1.1 and 16.2.5.1.2.

Pegcetacoplan was administered to 23 patients across the three parts of the study (A, B, and C), while 8 patients received placebo in Part A. The mean (SD) duration of pegcetacoplan treatment across the entire study was 324.9 days (171.5). The placebo group had a mean (SD) treatment duration of 151.6 days (34.5) in Part A.

In 95.7% of patients throughout the entire study, the administered dose matched the intended dose without any deviations. During Part A, treatment compliance was 100% in 15/16 patients (93.8%) on active and 6/8 patients (75.0%) on placebo. Overall, 16/23 patients (69.6%) receiving pegcetacoplan completed all planned infusions of pegcetacoplan. All patients in the placebo group (100%) completed all infusions of placebo without any interruptions. A total of 2132 pegcetacoplan infusions and 343 placebo infusions were administered during the study. Of these, 2127 (99.8%) pegcetacoplan infusions and 343 placebo infusions (100%) were completed.

A strong adherence to the treatment schedule was observed, with most patients receiving their infusions as planned. No interruptions were reported in the placebo group.

Table 12-1. Treatment Exposure by Treatment Group – Safety Set

Parameter	Part A		Parts A, B, and C
	Pegcetacoplan (N=16) n (%)	Placebo (N=8) n (%)	Overall Pegcetacoplan (N=23) n (%)
Duration of Treatment (Days)			
N	16	8	23
Mean (SD)	157.6 (32.92)	151.6 (34.48)	324.9 (171.54)
Median	166.0	165.0	333.0
Min, Max	35, 172	67, 166	35, 628
Patient Years Duration of Treatment			
Total	6.91	3.32	20.46
Total Study Drug Administered (mL)			
N	16	8	23
Mean (SD)	910.4 (185.04)	857.5 (190.47)	1852.9 (964.00)
Median	960.0	930.0	1918.0
Min, Max	220, 980	400, 960	220, 3500

Parameter	Part A		Parts A, B, and C
	Pegcetacoplan (N=16) n (%)	Placebo (N=8) n (%)	Overall Pegcetacoplan (N=23) n (%)
Patients with all infusions completed	12 (75.0%)	8 (100%)	16 (69.6%)
Patients with any infusion interrupted	2 (12.5%)	0	4 (17.4%)
Patients with a temporary interruption in a completed infusion	1 (6.3%)	0	2 (8.7%)
Patients with any infusions not completed and not interrupted	3 (18.8%)	0	4 (17.4%)
Total number of infusions given	729	343	2132
Total number of infusions completed	725 (99.5%)	343 (100%)	2127 (99.8%)
Total number of infusions interrupted and not completed	1 (0.1%)	0	2 (0.1%)
Total number of infusions interrupted and resumed and completed	1 (0.1%)	0	2 (0.1%)
Total number of infusions not completed and not interrupted	2 (0.3%)	0	1 (0.0%)

Source: Table 14.1.7.

Note: Duration of dosing (days) = Date of last dose of treatment - Date of first dose of treatment + 1.

SD=standard deviation; Max=maximum; Min=minimum.

12.2. Adverse Events

12.2.1. Brief Summary of Adverse Events

Treatment-emergent adverse events (TEAEs) were defined as those AEs that start on or after the first dose of IMP and up to 8 weeks after the last dose of study medication. An overview of TEAEs is presented in Table 12-2. A by-patient listing of TEAEs is provided in Listing 16.2.7.

Of 23 patients who received pegcetacoplan in Parts A, B, and C, one patient (4.3%) from Part A experienced a TESAE of Cholecystitis that led to death of the patient. This TESAE was severe in intensity and considered not related to the IMP.

Overall, 18 TESAEs were reported in 10/23 patients (43.5%) while treated with pegcetacoplan during the study or during the 8-week post-treatment window for treatment-emergence, with highest incidence observed in the pegcetacoplan group of Part A (5/16 patients [31.3%]). Only 1/8 patients (12.5%) receiving placebo during Part A experienced a TESAE. In addition, one patient in Parts B and C who received placebo in Part A experienced a TESAE.

Twenty of 23 pegcetacoplan-treated patients (87.0%) reported TEAEs. Notably, 100% of patients in Part A, including both the pegcetacoplan and placebo groups, reported TEAEs. The only identified infection by encapsulated bacteria - Enterococcal sepsis was reported in the Part A - pegcetacoplan group. Three of 23 patients (13.0%) receiving pegcetacoplan overall, reported TEAEs that led to premature discontinuation of the IMP, including 2 patients (12.5%) from Part A

- pegcetacoplan group. One patient (7.1%) who received pegcetacoplan during Part A had a TEAE leading to premature discontinuation of the IMP during Parts B and C.

All patients treated in this study reported at least 1 TEAE. The majority of TEAEs occurred in both treatment groups were of mild severity. Overall, 8/23 patients (34.8%) treated with pegcetacoplan at any time during the study reported TEAEs of up to moderate severity (5/16 patients [31.3%] in the pegcetacoplan group and 3/8 patients [37.5%] in the placebo group) and the same number (8/23 patients [34.8%]) of patients reported TEAEs of up to severe intensity (4/16 patients [25.0%] in the pegcetacoplan group and 1/8 patient [12.5%] in the placebo group) TEAEs during the study (Table 14.3.1.11).

Note: The period for reporting TEAEs ended 56 days (8 weeks) after the last dose of IMP. Any AEs identified after this period were not classified as treatment-emergent according to the definition set in the protocol. Some AEs including SAEs were captured and reported at later dates due to the windows for the last study visits. Such AEs were listed but not considered as TEAEs in the corresponding tables.

Table 12-2. Overview of Treatment-Emergent Adverse Events – Safety Population

Parameter	Part A		Parts B and C		Parts A, B, and C
	Pegcetacoplan (N=16) n (%)	Placebo (N=8) n (%)	Pegcetacoplan (Pegcetacoplan in Part A) (N=14) n (%)	Pegcetacoplan (Placebo in Part A) (N=7) n (%)	Overall Pegcetacoplan (N=23) n (%)
Patients with TEAEs	16 (100%)	8 (100%)	12 (85.7%)	4 (57.1%)	20 (87.0%)
Patients with TESAEs	5 (31.3%)	1 (12.5%)	6 (42.9%)	1 (14.3%)	10 (43.5%)
Patients with non-serious TEAEs	16 (100%)	8 (100%)	12 (85.7%)	4 (57.1%)	20 (87.0%)
Patients with TEAEs leading to premature discontinuation of IMP	2 (12.5%)	0	1 (7.1%)	0	3 (13.0%)
Patients with TEAEs leading to death	1 (6.3%)	0	0	0	1 (4.3%)
Patients with a Mild Severity TEAE	16 (100%)	7 (87.5%)	10 (71.4%)	3 (42.9%)	19 (82.6%)
Patients with a Moderate Severity TEAE	8 (50.0%)	4 (50.0%)	6 (42.9%)	3 (42.9%)	13 (56.5%)
Patients with a Severe TEAE	4 (25.0%)	1 (12.5%)	4 (28.6%)	0	8 (34.8%)
Patients with a Device-Related TEAE	1 (6.3%)	0	0	0	1 (4.3%)

Source: Table 14.3.1.1.

Note: TEAEs are coded using MedDRA version 27.1, September 2024.

MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.

12.2.2. Display of Adverse Events

Summary tables of TEAEs are listed in Section 14.3 and presented in detail in Section 12.2.3.

12.2.3. Analysis of Adverse Events

12.2.3.1. Adverse Events by Incidence

A summary of TEAEs by MedDRA SOC and PT that occurred in ≥3 patients by PT in the overall pegcetacoplan group is presented in Table 12-3. All TEAEs occurred in patients treated during the study are presented in Table 14.3.1.3. A summary of pre-treatment AEs by PT is presented in Table 14.2.1.2; summary of TEAEs by PT is presented in Table 14.3.1.4.

Overall, 20/23 patients (87.0%) from the combined Parts A, B, and C pegcetacoplan analysis group experienced at least 1 TEAE. All patients in Part A (pegcetacoplan and placebo groups) experienced at least 1 TEAE.

On SOC level, the most commonly reported TEAEs by SOC were General disorders and administration site conditions, Infections and infestations, and Blood and lymphatic disorders.

On PT level, the most frequently reported TEAEs (>10% in the overall pegcetacoplan group for Parts A, B, and C) by PT during or within 8 weeks of treatment with pegcetacoplan during Part A included Fatigue (3/16 patients [18.8%] in the pegcetacoplan group and none in the placebo group), Oedema peripheral (3/16 patients [18.8%] in the pegcetacoplan group and 3/8 patients [37.5%] in the placebo group), COVID-19 (3/16 patients [18.8%] in the pegcetacoplan group versus 2/8 patients [25.0%] in the placebo group), Upper respiratory tract infection (3/16 patients [18.8%] in the pegcetacoplan group and none in the placebo group in Part A), Pneumonia (1/16 patient [6.3%] in the pegcetacoplan group in Part A and none in the placebo group), and Cold type haemolytic anaemia (2/16 patients [12.5%] in the pegcetacoplan group and none in the placebo group). In the same population (>10% in the overall pegcetacoplan group for Parts A, B, and C), the commonly reported TEAEs (>10% of the population) in Parts B and C included COVID-19 (3/14 patients [21.4%]; previously treated with pegcetacoplan in Part A), Pneumonia (2/14 patients [14.3%]; previously treated with pegcetacoplan in Part A), and Cold type haemolytic anaemia (3/14 patients [21.4%]; previously treated with pegcetacoplan in Part A).

A summary of non-serious TEAEs by SOC and PT is provided in Table 14.3.1.5 and summary of non-serious TEAEs by PT is provided in Table 14.3.1.6.

Table 12-3. Summary of Treatment-Emergent Adverse Events Reported by ≥3 Patients Overall by System Organ Class and Preferred Term in the Overall Pegcetacoplan Group – Safety Set

	Part A		Parts B and C		Parts A, B, and C
System Organ Class/ Preferred Term	**Pegcetacoplan (N=16) n (%) EAIR**	**Placebo (N=8) n (%) EAIR**	**Pegcetacoplan (Pegcetacoplan in Part A) (N=14) n (%) EAIR**	**Pegcetacoplan (Placebo in Part A) (N=7) n (%) EAIR**	**Overall Pegcetacoplan (N=23) n (%) EAIR**
Patients with event	16 (100%) 1074	8 (100%) 864	12 (85.7%) 505	4 (57.1%) 160	20 (87.0%) 501
General disorders and administration site conditions	9 (56.3%) 178	4 (50.0%) 173	2 (14.3%) 20	1 (14.3%) 19	10 (43.5%) 63
Fatigue	3 (18.8%) 50	0	0	0	3 (13.0%) 15
Oedema peripheral	3 (18.8%) 46	3 (37.5%) 114	0	0	3 (13.0%) 13
Infections and infestations	8 (50.0%) 166	4 (50.0%) 155	7 (50.0%) 86	4 (57.1%) 160	16 (69.6%) 131
COVID-19	3 (18.8%) 48	2 (25.0%) 66	3 (21.4%) 30	0	5 (21.7%) 25
Upper respiratory tract infection	3 (18.8%) 47	0	1 (7.1%) 9	0	3 (13.0%) 14
Pneumonia	1 (6.3%) 14	0	2 (14.3%) 20	0	3 (13.0%) 13
Blood and lymphatic system disorders	3 (18.8%) 46	1 (12.5%) 32	6 (42.9%) 62	4 (57.1%) 108	13 (56.5%) 70
Cold type haemolytic anaemia	2 (12.5%) 30	0	3 (21.4%) 30	0	5 (21.7%) 24

Source: Table 14.3.1.3.

Notes:

Adverse Events were coded using MedDRA version 27.1, September 2024.

At each level of summarization, a patient was counted once if the patient reported one or more events.

EAIR = Exposure Adjusted Incidence Rate was calculated as (number of patients with AE during the study period or in the 56 day treatment-emergence follow-up after last treatment)/total person-years at risk during the study period)*100. Part B & C were considered a single period in this table.

The time at risk per patient was defined as time from first dose of IMP to last dose of IMP in the respective period + 56 days (for the last treatment), or death, if earlier, for those patients without a respective AE. For patients with the AE during the period, it was the time from first dose of IMP to AE start date during the period.

Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; EAIR=Exposure Adjusted Incidence Rate; IMP=investigational medicinal product; MedDRA=Medical Dictionary for Regulatory Activities.

12.2.3.2. Adverse Events by Severity

Table 14.3.1.11 summarizes TEAEs by PT and maximum severity. Overall, the majority of the TEAEs that occurred in both treatment groups were of mild severity. Overall, 8/23 patients (34.8%) treated with pegcetacoplan at any time during the study reported moderate (5/16 patients [31.3%] in the pegcetacoplan group and 3/8 patients [37.5%] in the placebo group) and severe (4/16 patients [25.0%] in the pegcetacoplan group and 1/8 patient [12.5%] in the placebo group) TEAEs each during the study. The severe TEAEs reported in pegcetacoplan-treated patients across the study included Cold type haemolytic anaemia (2 patients); Enterococcal sepsis, Gastrooesophageal haemorrhage, Haemangioma, Cholecystitis, Haemolytic anaemia, Pneumonia, Pelvic fracture, Syncope, and Haemolysis (all of them were reported in 1 patient each). Additionally, 1/8 patient (12.5%) from Part A – placebo group experienced a severe TEAE (Back pain) and 3/8 patients (37.5%) from Part A – placebo group experienced moderate TEAEs during Part A (Listing 16.2.7).

12.2.3.3. Adverse Events by Relationship

A summary of IMP-related TEAEs by PT is presented in Table 12-4. All IMP-related TEAEs by PT are summarized in Table 14.3.1.9 and summary of TESAEs related to the IMP by PT is provided in Table 14.3.1.10.

All patients from Part A (both treatment groups) reported at least one TEAE. A total of 7/23 patients (30.4%) treated with pegcetacoplan in Parts A, B, and C reported at least one TEAE related to the IMP. No related TEAEs of the same PT were reported in more than 1 patient.

Table 12-4. Summary of TEAEs Related to the IMP by Preferred Term

Preferred Term/ Intensity	Part A		Parts B and C		Parts A, B, and C
	Pegcetacoplan (N=16) n (%) EAIR	Placebo (N=8) n (%) EAIR	Pegcetacoplan (Pegcetacoplan in Part A) (N=14) n (%) EAIR	Pegcetacoplan (Placebo in Part A) (N=7) n (%) EAIR	Overall Pegcetacoplan (N=23) n (%) EAIR
Patients with at least one TEAE	16 (100%) 699	8 (100%) 807	12 (85.7%) 461	4 (57.1%) 160	20 (87.0%) 418
Related	6 (37.5%) 111	1 (12.5%) 32	2 (14.3%) 20	1 (14.3%) 23	7 (30.4%) 41
Fatigue	3 (18.8%) 50	0	0	0	3 (13.0%) 15
Related	1 (6.3%) 15	0	0	0	1 (4.3%) 5
Pruritus	2 (12.5%) 31	0	1 (7.1%) 10	0	2 (8.7%) 9
Related	1 (6.3%) 15	0	0	0	1 (4.3%) 4
Haemorrhage subcutaneous	1 (6.3%) 14	0	0	0	1 (4.3%) 4
Related	1 (6.3%) 14	0	0	0	1 (4.3%) 4
Induration	1 (6.3%) 14	0	0	0	1 (4.3%) 4
Related	1 (6.3%) 14	0	0	0	1 (4.3%) 4
Injection site paraesthesia	1 (6.3%) 14	0	0	0	1 (4.3%) 4
Related	1 (6.3%) 14	0	0	0	1 (4.3%) 4
Injection site pruritus	1 (6.3%) 14	0	0	0	1 (4.3%) 4
Related	1 (6.3%) 14	0	0	0	1 (4.3%) 4
Nausea	1 (6.3%) 15	0	0	0	1 (4.3%) 4
Related	1 (6.3%) 15	0	0	0	1 (4.3%) 4
Pain in extremity	1 (6.3%) 15	0	0	0	1 (4.3%) 4
Related	1 (6.3%) 15	0	0	0	1 (4.3%) 4
Cystitis	0	0	0	1 (14.3%) 23	1 (4.3%) 4
Related	0	0	0	1 (14.3%) 23	1 (4.3%) 4

Preferred Term/ Intensity	Part A		Parts B and C		Parts A, B, and C
	Pegcetacoplan (N=16) n (%) EAIR	Placebo (N=8) n (%) EAIR	Pegcetacoplan (Pegcetacoplan in Part A) (N=14) n (%) EAIR	Pegcetacoplan (Placebo in Part A) (N=7) n (%) EAIR	Overall Pegcetacoplan (N=23) n (%) EAIR
Gamma-glutamyl transferase increased	0	1 (12.5%) 32	0	0	0
Related	0	1 (12.5%) 32	0	0	0
Haemolysis	0	0	1 (7.1%) 9	1 (14.3%) 19	2 (8.7%) 8
Related	0	0	1 (7.1%) 9	0	1 (4.3%) 4
Injection site mass	0	0	1 (7.1%) 10	0	1 (4.3%) 4
Related	0	0	1 (7.1%) 10	0	1 (4.3%) 4

Source: Table 14.3.1.9.

Notes:

Adverse events were coded using MedDRA v27.1, September 2024.

At each level of summarization, a patient was counted once if the patient reported one or more events.

The first row for each preferred term presents data for all TEAEs and second row only related TEAEs.

EAIR = Exposure Adjusted Incidence Rate was calculated as (number of patients with AE during the study period or in the 56 days treatment-emergence follow-up after last treatment) / total person-years at risk during the study period) * 100. Part B and C were considered a single period in this table.

The time at risk per patient was defined as the time from first dose of IMP to last dose of IMP in the respective period + 56 days (for the last treatment), or death, if earlier, for those patients without a respective AE. For patients with the AE during the period, it was the time from first dose of IMP to AE start date during the period.

AE=adverse event; EAIR=Exposure Adjusted Incidence Rate; MedDRA=Medical Dictionary for Regulatory Activities; TEAEs=treatment-emergent adverse events.

12.2.4. Listing of Adverse Events by Patient

The following listing of AEs by patient is presented in Appendix 16.2.

Listing 16.2.7 Adverse Events – Safety Set

12.3. Deaths, Other Serious Adverse Events and Other Significant Adverse Events, and Adverse Events Leading to Treatment Discontinuation

12.3.1. Listings of Deaths, Other Serious Adverse Events and Other Significant Adverse Events, and Adverse Events Leading to Treatment Discontinuation

12.3.1.1. Deaths

One patient from Part A – pegcetacoplan group, aged 84 years at study entry, died due to a TESAE of severe Cholecystitis. The event was considered not related to pegcetacoplan. The outcome of the event was fatal (Table 14.3.1.1, Listing 16.2.7). Narrative of this event is provided in Section 12.3.2.

12.3.1.2. Other Serious Adverse Events

Table 12-5 provides information on the occurrence of TESAEs by-patient in each treatment group. A summary of TESAEs by PT is provided in Table 14.3.1.7. A by-patient listing of all TESAEs is provided in Listing 16.2.7.

A total of 10/23 patients (43.5%) treated with pegcetacoplan across three parts of the study, experienced 18 TESAEs (Listing 16.2.7). In Part A, 5/16 patients (31.3%) treated with pegcetacoplan experienced 6 TESAEs (COVID-19 pneumonia, Cholecystitis, Enterococcal sepsis, Haemolytic anaemia, Pneumonia, and Syncope), while 1/8 patients (12.5%) treated with placebo experienced 1 TESAE (COVID-19). In Parts B and C, 6/14 patients (42.9%) who were previously treated with pegcetacoplan in Part A experienced 12 TESAEs, while 1/7 patient (14.3%) who was previously treated with placebo in Part A experienced 1 TESAE.

The narratives for these events are provided in the Section 12.3.2.

Table 12-5. Summary of TESAEs by-Patient and Treatment Group – Safety Set

Patient ID	Start Date/ End Date/ Duration (Days)	Treatment Period	Study Part at the Start of the Event: A/B/C	Date of last dose administration	System Organ Class/ Preferred Term/ Verbatim Term	Outcome/ Severity	Relationship / Action taken with study drug
Treatment Group in Part A=Pegcetacoplan							
320301	08 Jan 2024 (Study Day 36)/ 17 Jan 2024 (Study Day 45)/ 9	04 Dec 2023 to 01 Jul 2024	Part A	01 Jul 2024	Infections and infestations/ **Enterococcal sepsis**/ Sepsis with doucmented bactiremia e.faecalis digestive origin	Recovered/ Resolved/ Severe	Not Related/ Not Applicable
340101	29 Jul 2024 (Study Day 533)	13 Feb 2023 to 04 Jul 2024	After Part C (during follow-up)	04 Jul 2024	Blood and lymphatic system disorders/ Cold type haemolytic anaemia/ Agglutinin disease worsening	Not Recovered/ Not Resolved/ Severe	Not Related/ Not Applicable
430102	24 Jul 2024 (Study Day 644)/ 25 Jul 2024 (Study Day 645)/ 1	20 Oct 2022 to 01 Apr 2024	After Part C (during follow-up)	01 Apr 2024	Blood and lymphatic system disorders/ Autoimmune haemolytic anaemia/ Mixed autoimmune haemolytic anaemia	Recovered/ Resolved/ Moderate	Not Related/ Not Applicable
	26 Jul 2024 (Study Day 646)/ 02 Aug 2024 (Study Day 653)/ 7	20 Oct 2022 to 01 Apr 2024	After Part C (during follow-up)	01 Apr 2024	Blood and lymphatic system disorders/ Autoimmune haemolytic anaemia/ Mixed autoimmune haemolytic anaemia	Recovered/ Resolved/ Moderate	Not Related/ Not Applicable
430103	20 Aug 2023 (Study Day 286)/ 24 Aug 2023 (Study Day 290)/ 4	08 Nov 2022 to 31 Oct 2023	Part B	31 Oct 2023	Renal and urinary disorders/ **Acute kidney injury**/ Acute renal failure	Recovered/ Resolved/ Moderate	Not Related/ Not Applicable
	26 Aug 2023 (Study Day 292)/ 12 Sep 2023 (Study Day 309)/ 17	08 Nov 2022 to 31 Oct 2023	Part B	31 Oct 2023	Cardiac disorders/ **Cardiac failure**/ Cardiac decompensation	Recovered/ Resolved/ Moderate	Not Related/ Not Applicable

Patient ID	Start Date/ End Date/ Duration (Days)	Treatment Period	Study Part at the Start of the Event: A/B/C	Date of last dose administration	System Organ Class/ Preferred Term/ Verbatim Term	Outcome/ Severity	Relationship / Action taken with study drug
	23 Oct 2023 (Study Day 350)/ 31 Oct 2023 (Study Day 358)/ 8	08 Nov 2022 to 31 Oct 2023	Part C	31 Oct 2023	Blood and lymphatic system disorders/ **Cold type haemolytic anaemia**/ Worsening of CAD anaemia	Recovered/ Resolved/ Moderate	Not Related/ Not Applicable
	11 Nov 2023 (Study Day 369)/ 28 Nov 2023 (Study Day 386)/ 17	08 Nov 2022 to 31 Oct 2023	After Part C (during follow-up)	31 Oct 2023	Blood and lymphatic system disorders/ Cold type haemolytic anaemia/ Symptomatic CAD anaemia	Recovered/ Resolved/ Moderate	Not Related/ Drug Withdrawn
	28 Dec 2023 (Study Day 416)/ 07 Jan 2024 (Study Day 426)/ 10	08 Nov 2022 to 31 Oct 2023	After Part C (during follow-up)	31 Oct 2023	Infections and infestations/ Pneumonia/ Pneumonia (left)	Recovered/ Resolved/ Moderate	Not Related/ Drug Withdrawn
440102	28 Jul 2023 (Study Day 158)/ 29 Jul 2023 (Study Day 159)/ 1	21 Feb 2023 to 25 Jul 2023	After Part A (during follow-up)	25 Jul 2023	Hepatobiliary disorders/ **Cholecystitis**/ Cholecystitis	Fatal/ Severe	Not Related/ Drug Withdrawn
440103	06 Apr 2023 (Study Day 38)/ 28 Apr 2023 (Study Day 60)/ 22	28 Feb 2023 to 03 Apr 2023	After Part A (during follow-up)	03 Apr 2023	Blood and lymphatic system disorders/ **Haemolytic anaemia**/ Severe aneamia (worsening of haemolytic anaemia)	Recovered/ Resolved/ Severe	Not Related/ Drug Withdrawn
	08 May 2023 (Study Day 70)/ 26 May 2023 (Study Day 88)/ 18	28 Feb 2023 to 03 Apr 2023	After Part A (during follow-up)	03 Apr 2023	Infections and infestations/ **Pneumonia**/ Hospital acquired pneumonia	Recovered/ Resolved/ Severe	Not Related/ Not Applicable

Patient ID	Start Date/ End Date/ Duration (Days)	Treatment Period	Study Part at the Start of the Event: A/B/C	Date of last dose administration	System Organ Class/ Preferred Term/ Verbatim Term	Outcome/ Severity	Relationship / Action taken with study drug
490101	01 Oct 2023 (Study Day 45)/ 09 Oct 2023 (Study Day 53)/ 8	18 Aug 2023 to 09 Jul 2024	Part A	09 Jul 2024	Nervous system disorders/ **Syncope**/ Syncope	Recovered/ Resolved/ Severe	Not Related/ Not Applicable
	21 Jul 2024 (Study Day 339)/ 27 Aug 2024 (Study Day 376)/ 37	18 Aug 2023 to 09 Jul 2024	After Part B (during follow-up)	09 Jul 2024	Blood and lymphatic system disorders/ Breakthrough haemolysis/ Breaktrough haemolysis	Recovered/ Resolved/ Moderate	Not Related/ Not Applicable
	08 Aug 2024 (Study Day 357)/ 14 Aug 2024 (Study Day 363)/ 6	18 Aug 2023 to 09 Jul 2024	After Part B (during follow-up)	09 Jul 2024	Cardiac disorders/ Atrial fibrillation/ Worsening of atrial fibrillation	Recovered/ Resolved/ Moderate	Not Related/ Not Applicable
810302	12 Jul 2023 (Study Day 107)/ 22 Jul 2023 (Study Day 117)/ 10	28 Mar 2023 to 11 Jun 2024	Part A	11 Jun 2024	Infections and infestations/ **COVID-19 pneumonia**/ COVID-19 pneumonia	Recovered/ Resolved/ Moderate	Not Related/ Not Applicable
	08 Sep 2023 (Study Day 165)/ 04 Oct 2023 (Study Day 191)/ 26	28 Mar 2023 to 11 Jun 2024	Part B	11 Jun 2024	Musculoskeletal and connective tissue disorders/ **Osteonecrosis of jaw**/ Osteonecrosis of jaw	Recovered/ Resolved/ Mild	Not Related/ Drug Interrupted
810401	17 Jul 2024 (Study Day 280)	12 Oct 2023 to 08 Jul 2024	After Part B (during follow-up)	08 Jul 2024	Blood and lymphatic system disorders/ Haemolysis/ Hemolysis	Not Recovered/ Not Resolved/ Severe	Related/ Not Applicable

Patient ID	Start Date/ End Date/ Duration (Days)	Treatment Period	Study Part at the Start of the Event: A/B/C	Date of last dose administration	System Organ Class/ Preferred Term/ Verbatim Term	Outcome/ Severity	Relationship / Action taken with study drug
Treatment Group in Part A = Placebo							
430104	31 Jul 2024 (Study Day 553)/ 07 Aug 2024 (Study Day 560)/ 7	26 Jan 2023 to 08 Jul 2024	After Part C (during follow-up)	08 Jul 2024	Blood and lymphatic system disorders/ Autoimmune haemolytic anaemia/ Mixed autoimmune haemolytic anaemia	Recovered/ Resolved/ Moderate	Not Related/ Not Applicable
950103	17 Apr 2023 (Study Day 84)/ 27 Apr 2023 (Study Day 94)/ 10	24 Jan 2023 to 09 Jul 2024	Part A	09 Jul 2024	Infections and infestations/ **COVID-19**/ COVID-19 infection	Recovered/ Resolved/ Mild	Not Related/ Drug Interrupted

Source: Listing 16.2.7.

Note: Adverse events were coded by MedDRA v27.1, September 2024.

The PTs in bold occurred during the treatment period.

CAD=Cold Agglutinin Disease; COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAE=serious adverse event.

A summary of TESAEs related to the IMP by PT is summarized in Table 14.3.1.10. During the study, 1/23 patient (4.3%) treated with pegcetacoplan across all parts of the study experienced a TESAE of Haemolysis, which was deemed to be related to the IMP by the investigator and not related to the IMP by the sponsor. The TESAE of Haemolysis was severe in intensity and was treated with blood transfusion (Listing 16.2.7).

12.3.1.3. Other Significant Adverse Events

Table 14.3.1.13 summarizes TEAEs of special interest (TEAESIs), including injection site reactions and infections by treatment group and PT. A total of 18/23 patients (78.3%) treated with pegcetacoplan in Parts A, B, and C, with 11/16 patients (68.8%) treated with pegcetacoplan in Part A and 4/8 patients (50.0%) treated with placebo in Part A reported TEAESI during the study.

Table 12-6 summarizes injection site reaction TEAEs by treatment group and PT. A total of 6 injection site TEAEs were reported in 4/16 patients (25.0%) receiving pegcetacoplan in Part A compared with 0/8 patients (0%) receiving placebo. Two of 16 patients (12.5%) in the pegcetacoplan group had more than 1 TEAESIs related to the injection site reaction. All of these events were reported to be related to pegcetacoplan, except injection site swelling. No injection site TEAEs were reported in the placebo group. A by-patient listing of infusion site assessment is provided in Listing 16.4.12.

Table 12-6. Summary of Injection Site Reaction TEAEs by Treatment Group and PT – Safety Set

Preferred Term	Pegcetacoplan (N=16) n (%)	Placebo (N=8) n (%)
Patients with event	4 (25.0%)	0
Haemorrhage subcutaneous	1 (6.3%)	0
Induration	1 (6.3%)	0
Injection site mass	1 (6.3%)	0
Injection site paraesthesia	1 (6.3%)	0
Injection site pruritus	1 (6.3%)	0
Injection site swelling	1 (6.3%)	0

Source: Table 14.3.1.12.

Notes:

Adverse events were sorted by decreasing frequency in the pegcetacoplan group.

Adverse events were coded using MedDRA v27.1, September 2024.

MedDRA=Medical Dictionary for Regulatory Activities.

Table 12-7 provides a summary of all TEAESIs of infections by treatment group and PT. The most frequently reported TEAESIs of infections (≥10% patients total) included COVID-19 (21.7% in pegcetacoplan overall versus 25.0% in placebo groups with an EAIR of 48 cases per 100 persons year in the pegcetacoplan group during the randomized controlled Part A [3/16 patients {18.8%}] as compared to 66 cases per 100 persons year in the placebo group [2/8 patients {25.0%}]), followed by Upper respiratory tract infection (13.0% overall from Part A – pegcetacoplan group with an EAIR of 47 cases per 100 persons year during the randomized controlled period Part A [3/16 patients {18.8%}] and 14 cases per 100 persons year during the full period patients remained on pegcetacoplan [3/23 patients {13.0%}]), and Pneumonia (13.0% in pegcetacoplan overall, with 1/16 patient [6.3%] in Part A – pegcetacoplan group and 2/14 patients [14.3%] from Parts B and C [received pegcetacoplan in Part A] with an EAIR of 14 cases per 100 persons year during the randomized controlled period Part A and 13 cases per 100 persons year during the full period patient remained on pegcetacoplan).

Table 12-7. Summary of TEAEs of Special Interest by Treatment Group and Preferred Term – Safety Set

Preferred Term	Part A		Parts A, B, and C
	Pegcetacoplan (N=16) n (%) EAIR	Placebo (N=8) n (%) EAIR	Overall Pegcetacoplan (N=23) n (%) EAIR
COVID-19	3 (18.8%) 48	2 (25.0%) 66	5 (21.7%) 25
Upper respiratory tract infection	3 (18.8%) 47	0	3 (13.0%) 14
Bacteriuria	1 (6.3%) 15	0	1 (4.3%) 4

Preferred Term	Part A		Parts A, B, and C
	Pegcetacoplan (N=16) n (%) EAIR	Placebo (N=8) n (%) EAIR	Overall Pegcetacoplan (N=23) n (%) EAIR
Bronchitis	1 (6.3%) 15	0	1 (4.3%) 4
COVID-19 pneumonia	1 (6.3%) 14	0	1 (4.3%) 4
Enterococcal sepsis	1 (6.3%) 15	0	1 (4.3%) 4
Nasopharyngitis	1 (6.3%) 14	0	2 (8.7%) 9
Oral herpes	1 (6.3%) 14	0	1 (4.3%) 4
Osteomyelitis	1 (6.3%) 14	0	1 (4.3%) 4
Pneumonia	1 (6.3%) 14	0	3 (13.0%) 13
Respiratory tract infection	1 (6.3%) 14	0	1 (4.3%) 4
Cystitis	0	0	1 (4.3%) 4
Fungal skin infection	0	1 (12.5%) 31	0
Influenza	0	1 (12.5%) 29	1 (4.3%) 4
Rhinitis	0	0	1 (4.3%) 4
Sinusitis	0	0	1 (4.3%) 4
Urinary tract infection	0	1 (12.5%) 29	2 (8.7%) 9

Source: Table 14.3.1.13.

Notes:

Adverse events were coded using MedDRA v27.1, September 2024.

At each level of summarization, a patient was counted once if the patient reported one or more events.

EAIR = (number of patients with AE during the study period or in the 56-day treatment-emergence follow-up after last treatment) / total person-years at risk during the study period) * 100.

The time at risk per patient is defined as time from first dose of IMP to last dose of IMP in the respective period + 56 days (for the last treatment), or death, if earlier, for those patients without a respective AE. For patients with the AE during the period, it is the time from first dose of IMP to AE start date during the period.

AE=adverse event; COVID-19=coronavirus disease 2019; EAIR=Exposure Adjusted Incidence Rate; IMP=investigational medicinal product; MedDRA=Medical Dictionary for Regulatory Activities; TEAESI=treatment-emergent adverse event of special interest.

12.3.1.4. Adverse Events Leading to Treatment Discontinuation

Table 14.3.1.8 provides a summary of TEAEs that led to premature discontinuation of IMP by PT. In total, 10 TEAEs led to premature IMP discontinuation in three patients, with two of them from Part A – pegcetacoplan group. The TEAEs that contributed towards the discontinuation of IMP in Part A included: Atrial fibrillation, Cardiac failure, Cholecystitis, Haemolytic anaemia, Pleural effusion, Pneumonia, Respiratory failure, and Scrotal oedema. Additionally, one patient from Parts B and C, who had received pegcetacoplan in Part A, was discontinued from the study treatment due to the event of Cold type haemolytic anaemia. No treatment discontinuations

occurred in the placebo group. The narratives for the events that led to study treatment discontinuation are included in Section 12.3.2.

Note: The total number of reported TEAEs leading to IMP discontinuation was 10 based on Listing 16.2.7, compared to 9 TEAEs in Table 14.3.1.8. The reason for this discrepancy was that one event of Pneumonia (per Listing 16.2.7) had an onset date 58 days after the last dose of the IMP, making it ineligible to be classified as a TEAE. The study Protocol (Section 6.5.4.1.2 Adverse Event Reporting Period) states that TEAEs with onset more than 8 weeks after the last IMP administration need to be reported only if serious and considered causally related to previous exposure to the IMP by the investigator. Hence, this TEAE was retained in the listings for fidelity to the CRF data but was not counted as a TEAE in the summary table.

12.3.2. Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Narratives of deaths, other TESAEs, certain other significant TEAEs, and TEAEs leading to treatment discontinuation were reported in the Section 14.3.3.

12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

One patient died due to a TESAE of Cholecystitis. Overall, 18 TESAEs occurred in 10/23 patients (43.5%) treated with pegcetacoplan; one patient from the placebo group experienced a TESAE of COVID-19. Additionally, one TESAE of Haemolysis reported in Parts B and C (with patient receiving pegcetacoplan in Part A) reported as related to the IMP, and all other events were assessed as not related. Higher incidence of TEAESIs was reported in Part A pegcetacoplan group (78.3%) compared to the placebo group (50.0%). A total of 6 injection site TEAEs were reported in 4 pegcetacoplan-treated patients in Part A (25.0%), with 5 TEAEs being related to pegcetacoplan. The most frequently reported TEAESIs were COVID-19, Upper respiratory tract infection, and Pneumonia.

12.4. Clinical Laboratory Evaluation

12.4.1. Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

The following listings of laboratory measurements are presented

Listing 16.2.8.1	Hematology Laboratory Results – Safety Set
Listing 16.2.8.2	Serum Chemistry Results – Safety Set
Listing 16.2.8.3	Urine Analysis Results – Safety Set
Listing 16.2.8.4	Coagulation Results – Safety Set
Listing 16.2.8.5	Immunogenicity Data – Safety Set
Listing 16.3.1	Complement Biomarkers – PD Set
Listing 16.3.2	Inflammatory Biomarkers – PD Set

Listing 16.4.13	Pregnancy Test – Safety Set

12.4.2. Evaluation of Laboratory Parameters

12.4.3. Hematology

Observed values and changes from Baseline for hematology are summarized in Table 14.3.4.1. A by-patient listing on hematology laboratory results is provided in Listing 16.2.8.1. A plot of mean (SD) changes from Baseline in Hb is presented in Figure 14.2.1.1.

Most changes from Baseline in hematology parameters were small and not clinically meaningful, except the change in Hb. As anticipated in this population, decreased values of Hb and hematocrit as well as platelet counts were observed in all patients at some point during the study. Increased and decreased values of reticulocyte count were also observed. However, none of these changes were considered clinically meaningful by the investigator. With pegcetacoplan, an improvement was observed with Hb and hematocrit values from Baseline over time during the study.

At Baseline, 6/16 patients (37.5%) patients from the pegcetacoplan group and 2/8 patients (25.0%) from the placebo group had low Hb levels graded ≥3 by CTCAE. With pegcetacoplan, majority of these clinical abnormalities were resolved by Week 24. The TEAEs related to low Hb levels later in the study included Cold type haemolytic anaemia, Haemolytic anaemia, Anaemia, Autoimmune haemolytic anaemia, and Warm autoimmune haemolytic anaemia (Table 14.3.4.5). One TEAE of Platelet count increased occurred in Parts B and C (pegcetacoplan in Part A) and one TEAE of Thrombocytosis in placebo group was recorded. Both TEAEs were of mild severity, assessed to be not related to IMP, and were recovered/resolved.

12.4.4. Serum chemistry

A summary of changes from Baseline in serum chemistry values is provided in Table 14.3.4.2. Biochemistry abnormalities of CTCAE Grade ≥3 by study week until 8 weeks after EOT are tabulated in Table 14.3.4.6. By-patient listings of serum chemistry levels is provided in Listing 16.2.8.2.

No meaningful changes in the serum chemistry values were identified other than those reported as potential hints for efficacy in the corresponding section of this CSR. Two serum chemistry related TEAEs, one of Hypoglycaemia in the pegcetacoplan group and one of Gamma-glutamyl transferase increased in the placebo group were recorded in Part A. Both were of mild severity and were recovered/resolved. The TEAE of Hypoglycaemia was considered as not related to the IMP, while the TEAE of Gamma-glutamyl transferase increased was considered as related to the IMP.

12.4.5. Urinalysis

Table 14.3.4.3 summarizes the observed values and change from Baseline in urine analysis parameters. The urinalysis abnormalities of CTCAE Grade ≥3 by study week are provided in Table 14.3.4.7. By-patient results of urine analysis results is provided in Listing 16.2.8.3. The changes from Baseline in urinalysis results were small and not clinically meaningful. No TEAEs related to urinalysis parameters were reported in this study (Table 14.3.1.4; Table 14.3.4.7).

12.4.6. Coagulation

Table 14.3.4.4 summarizes the observed and change from Baseline values of coagulation parameters. By-patient results of coagulation parameters are provided in Listing 16.2.8.4. No clear changes from Baseline were noted in coagulation parameters. A reduction in D-dimer levels was seen in both treatment groups, with pegcetacoplan displaying higher reduction comparatively. Two TEAEs related to coagulation panel were identified; Thrombin-antithrombin III complex increased in the pegcetacoplan group of Part A and TEAE of Hypoprothrombinaemia in Parts B and C – previously on placebo. Both TEAEs were of mild severity, recovered/resolved, and were considered as not related to the IMP.

12.4.7. Immunogenicity

Note: During the study, two biological samples (each from Patients 440103 and 390402) were delivered to the central laboratory in a refrigerated condition instead of being frozen, as required for ADA, PK, and PD (cytokines and complement markers). These samples were subsequently frozen at the central laboratory before being sent to the bioanalytical laboratory for their respective analyses. Patient 390402 was a screen failure. Further details regarding this process deviation in Patient 440103 are provided in the NTF included in the Appendix 16.19.

12.4.7.1. ADA to Pegcetacoplan Peptide Moiety

Table 14.3.7.1 provides a summary of ADA to pegcetacoplan peptide moiety by treatment group. Figure 14.3.1.2 shows individual pegcetacoplan trough serum concentrations during the study by ADA positivity to pegcetacoplan peptide on a linear scale. A plot of individual ADA titers to pegcetacoplan peptide during the study is provided on a semi-logarithmic scale in Figure 14.3.1.11. By-patient listing of immunogenicity data was provided in Listing 16.2.8.5.

No patients had ADA to pegcetacoplan peptide moiety at Baseline. Post-baseline ADA incidence was detected in 3/16 patients (18.8%) from the pegcetacoplan group and 1/8 patients (12.5%) initially assigned to placebo, but while receiving pegcetacoplan during Part B and C. All three TEADAs reported in the pegcetacoplan patients were transient with a duration of 50 to 114 days, while the ADAs observed in the patient initially assigned to placebo was assigned as persistent since last time point was ADA positive with no further results available, but follow-up only lasted for 57 days after ADA detection. The time to onset of ADAs ranged from 162 to 227 days in the patients on pegcetacoplan. In the patient initially on placebo, ADAs were first detected on Study Day 253, i.e., 84 days after start of pegcetacoplan. The maximum TEADA titer was between 1:25 and 1:100 in the patients assigned to pegcetacoplan and 1:200 in the patient initially assigned to placebo. No NAbs were recorded in the pegcetacoplan treated patients; however, the ADA positive patient initially assigned to placebo had a single positive sample for NAb, detected after having received pegcetacoplan and 57 days after ADA detection (which was negative for Nab).

Figure 14.3.1.2 does not suggest any systematic trend on the trough concentrations of pegcetacoplan related to anti peptide moiety ADA positivity.

Only a limited proportion (18.8%) of patients developed TEADA and only one patient developed NAbs to the peptide. No AEs clearly related to the ADA to the peptide moiety were found. The period where ADAs might have been present is from the last negative sample before the first positive sample to the first negative sample thereafter (period at risk). From the 3 patients with TEADA to the peptide moiety, Patient 340501 had no AEs reported during the period at risk. For

Patient 430103, AEs reported during the period at risk were moderate, unspecific and the temporal relationship does not suggest a link. These AEs included a headache lasting a single day, 10 days before first detection; Performance status decreased 37 days after the last positive sample and 17 days before the first negative sample reverting 3 days after the first negative sample; Benign prostate hyperplasia diagnosed 43 days after the last positive sample and 11 days before the first negative sample, and Cold type haemolytic anaemia reported 47 days after the last positive sample and lasting until 67 days after the first negative sample). In Patient 810302, only Osteomyelitis and a linked Osteonecrosis of the jaw with clear local risk factors were reported in the period at risk of ADA. Hence, the detected ADAs to the peptide moiety do not appear to have resulted in any safety issues.

12.4.7.2. ADA to Polyethylene Glycol Moiety

A summary of ADA to PEG by treatment group is tabulated in Table 14.3.7.2. Figure 14.3.1.3 illustrates individual pegcetacoplan trough serum concentrations during the study by ADA positivity in polyethylene glycol – linear scale. Figure 14.3.1.12 depicts summary of individual ADA titers to PEG during the study on a semi-logarithmic scale.

Figure 14.3.1.3 does not suggest any systematic trend on the trough concentrations of pegcetacoplan related to anti PEG moiety ADA positivity.

At Baseline, 13/16 patients (81.3%) in pegcetacoplan group and 6/8 patients (75.0%) in placebo group had ADA to PEG moiety, with a median titer of 1:40 and 1:15, respectively. In pegcetacoplan group, post-baseline ADA incidence was same as that of Baseline, and in the group initially assigned to placebo, one additional patient developed ADA post-baseline, adding up to 7/8 patients (87.5%). One patient (6.3% in pegcetacoplan group versus 12.5% in placebo group) in each treatment group had TEADA. The TEADA in pegcetacoplan-treated patient was assigned as persistent (since last time point was ADA positive with no further results available), while it was transient in the placebo group patient. The time to onset of TEADA was 49 days and 14 days for the patient treated with pegcetacoplan and initially assigned to placebo, respectively. Two patients in each treatment group (12.5% in the pegcetacoplan and 25.0% in the placebo group) reported TBADA incidence, with a maximum titer increase of 8 times Baseline in pegcetacoplan-treated patients and of 4- and 8- times Baseline in the initially treated placebo patients. The median time to boosting of ADA was 67 days for the patients treated with pegcetacoplan and 124.5 days for patients initially treated with placebo.

The proportion of patients with Baseline ADA to the PEG moiety was high as expected, with reported prevalences of anti-PEG antibodies of up to 97.5% in the literature even in healthy blood donors, probably due to the many products containing PEG in frequent use such as many cosmetics and foods as well as the Spikevax® and Comirnaty® COVID-19 vaccines (Gaballa 2024) but only limited additional development of ADAs to the PEG moiety was observed during the study.

The development of ADAs to the PEG moiety was apparently not associated with any safety event among the patients with TEADA to the PEG moiety.

- The TEADA to the PEG moiety observed in Patient 440103 were only detected at an early termination visit obtained 20 days after a negative sample while the reported AEs do not include events suggesting hypersensitivity. The reported AEs were a group of events including a Pneumonia with Heart failure complications and CAD aggravation, started

twelve days before the date of the positive sample and appear attributable to the patient underlying condition (see patient narrative in Section 14.3.3).

- In the other patient (Patient 310202) with TEADA to the PEG moiety were only transiently detected while the patient was on placebo during Part A.

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1. Physical Examination

A by-patient listing of physical examination results by visit and treatment group is provided in Listing 16.4.15.

12.5.2. Vital Signs

Vital sign measurements included systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Vital signs measurements and their timing are described in Section 9.7.4.4. Vital sign normal ranges were defined as systolic BP of 90-120 mmHg, diastolic BP of 60-80 mmHg, heart rate of 60-100 bpm, respiratory rate of 12-18 bpm, and body temperature of 36.5-37.3 C.

Table 14.3.5.2 presents vital sign results and change from Baseline by treatment group and visit. Vital sign abnormalities by study week until 8 weeks after EOT are tabulated in Table 14.3.5.1. By-patient listing on vital sign measurements is provided in Listing 16.4.16. One clinically meaningful abnormal vital sign observation was made in association with an AE of Haemolysis.

Three TEAEs related to vital sign abnormalities were recorded as below (Listing 16.4.16):

- One TEAE of Hypotension (moderate severity) was reported in Part A – pegcetacoplan group, which was considered as not related to the IMP.
- One TEAE of Pyrexia (mild severity) was reported in Part A – pegcetacoplan group, which was considered as not related to the IMP.
- One TEAE of Hypertension (mild severity) was reported in Parts B and C (received pegcetacoplan in Part A), which was considered as not related to the IMP.

12.5.3. Electrocardiograms

A summary of ECG results buy visit and treatment group is presented in Table 14.3.6.1. By-patient listing of ECG is provided in Listing 16.4.9. No clinically relevant abnormal changes in the ECG results were observed throughout the study. Two TEAEs of Atrial fibrillation were reported as below:

- One TEAE of Atrial fibrillation of moderate severity in 1/16 patients (6.3%) from pegcetacoplan group of Part A. The event was considered as not related to the IMP and the IMP was withdrawn because of the event (Listing 16.2.7).
- One TEAE of Atrial fibrillation of moderate severity in 1/14 patients (7.1%) in Parts B and C (previously on pegcetacoplan in Part A). The event was considered as not related to the IMP (Listing 16.2.7).

12.6. Safety Conclusions

12.6.1. Summary of Safety Results

- Due to the early termination of the study, no Week 96 assessments were performed.
- A total of 20/23 pegcetacoplan-treated patients (87.0%) reported TEAEs, with all patients experiencing TEAEs during Part A. Majority of the TEAEs were of mild severity.
- A total of 7/23 patients (30.4%) treated with pegcetacoplan in Parts A, B, and C reported at least one TEAE related to the IMP. No related TEAEs of the same PT were reported in more than 1 patient.
- Overall, 18 TESAEs were reported in 10/23 patients (43.5%) while treated with pegcetacoplan during the study, with the highest incidence observed in the pegcetacoplan group of Part A (5/16 patients [31.3%]). Only one TESAE of COVID-19 infection was reported in the placebo group of Part A.
- One patient (4.3%) from Part A – pegcetacoplan group died due to a TESAE of Cholecystitis (severe and considered as not related to pegcetacoplan).
- The most commonly reported TEAEs by SOC were General disorders and administration site conditions, Infections and infestations, and Blood and lymphatic disorders. The most frequently reported TEAEs by PT that occurred in Part A during or within 8 weeks of treatment with pegcetacoplan included Fatigue, Oedema peripheral, COVID-19, Upper respiratory tract infection, and Cold type haemolytic anemia.
- Ten TEAEs led to premature discontinuation of pegcetacoplan in 3/23 patients (13.0%; 2 patients from Part A – pegcetacoplan group and 1 patient from Parts B and C – previously treated with pegcetacoplan in Part A). The TEAEs that led to the discontinuation of IMP in Part A included Atrial fibrillation, Cardiac failure, Cholecystitis, Haemolytic anaemia, Pleural effusion, Pneumonia, Respiratory failure, and Scrotal oedema. One patient from Parts B and C, who had received pegcetacoplan in Part A, was discontinued from the study treatment due to the event of Cold type haemolytic anaemia. No treatment discontinuations occurred in the placebo group.
- The overall incidence of TEAESI was higher in pegcetacoplan-treated patients (78.3%) compared with placebo (50.0%). Six injection site TEAEs were reported in 4/16 patients (25.0%) receiving pegcetacoplan in Part A compared with 0/8 patients (0%) receiving placebo, Injection site TEAEs included Haemorrhage subcutaneous, Induration, Injection site mass, Injection site paraesthesia, Injection site pruritus, and Injection site swelling. All these events were considered to be related to pegcetacoplan, except for Injection site swelling. The proportion of patients reporting TEAEs within the SOC of infections was equal in both arms during Part A (50.0%), with the only identified infection by encapsulated bacteria (Enterococcal sepsis, also a TESAE and was considered as not related to the IMP by the investigator and sponsor) occurring in the pegcetacoplan arm. Infections, especially respiratory tract infections, were common in both treatment groups, with a higher incidence observed in patients treated with pegcetacoplan.
- Most of the changes from Baseline in hematology parameters, except for Hb that improved in the pegcetacoplan arm and ARC that improved in both treatment arms, were small and not

clinically meaningful. The TEAEs of abnormal hematological parameters included Cold type acute haemolytic anaemia, Haemolytic anaemia, Anaemia, Autoimmune haemolytic anaemia, and Warm autoimmune haemolytic anaemia, Thrombocytopenia, and Platelet count increased.

- No clinically meaningful changes in the serum chemistry (other than decreases in LDH and in the pegcetacoplan group on indirect bilirubin and increases in haptoglobin in CAD group potentially related to CAD improvement) and urinalysis values were identified during the study. Two TEAEs of Hypoglycaemia and Gamma-glutamyl transferase increased were recorded in Part A – Hypoglycaemia in the pegcetacoplan group, Gamma-glutamyl transferase increased in the placebo group. These TEAEs were of mild severity and recovered/resolved. The TEAE of Hypoglycaemia was considered as not related to the IMP, while the TEAE of Gamma-glutamyl transferase increased was considered as related to the IMP. No TEAEs related to abnormal urinalysis were reported.
- Two TEAEs related to coagulation panel were identified; Thrombin-antithrombin III complex increased in pegcetacoplan group of Part A and TEAE of Hypoprothrombinaemia in Parts B and C – previously on placebo. Both TEAEs were of mild in severity, recovered/resolved, and were considered as not related to the IMP. The coagulation test results were comparable between the two groups.
- No ADAs to pegcetacoplan peptide moiety were observed at baseline. TEADAs incidence was 18.8% (3/16 patients) in Part A - pegcetacoplan group and 12.5% (1/8 patient) in patients initially on placebo, but TEADAs were found when the patient had already started treatment with pegcetacoplan. The overall incidence of ADA remained relatively low and NAb were found in a single sample.
- The ADA to PEG were common at Baseline, the incidence of TEADA and TBADA was relatively low, and the majority of TEADA cases were transient.
- Three TEAEs of abnormal vital sign parameters were recorded, including Hypotension (moderate), Pyrexia (mild), and Hypertension (mild). One clinically meaningful abnormal vital sign observation was made in association with a TEAE of Haemolysis.
- No clinically relevant abnormal findings were noted in the ECGs. Two TEAEs of Atrial fibrillation occurred in 2 patients, 1 patient from Part A – pegcetacoplan group and other from Parts B and C (received pegcetacoplan during Part A). Both TEAEs were moderate in severity and considered not related to the IMP.

12.6.2. Conclusions

Overall, the safety profile in the pegcetacoplan group remained consistent with what was anticipated in the CAD population, with a substantial number of patients experiencing mild TEAEs. Safety findings are in line with the expectations in this elderly population that often has concomitant conditions in addition to underlying disease CAD as well as with the known safety profile of pegcetacoplan. No unexpected findings or findings constituting a new safety signal in this analysis were identified.

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1. Discussion

This was a Phase 3, randomized, double-blind, placebo-controlled multicenter study of pegcetacoplan in patients with CAD. There were no approved or available therapies for patients with CAD in need of treatment at the time of study initiation, therefore placebo was chosen as a comparator (only for Part A of the study). The study was conducted at 49 centers in 15 countries.

In Part A, at Screening, the patients were randomized in a 2:1 ratio to receive either pegcetacoplan or placebo. In Parts B and C, all ongoing patients received only pegcetacoplan. Both IMPs were administered by SC infusion twice weekly. Overall, 24 patients were randomized, of whom 16 patients received pegcetacoplan and 8 patients received placebo.

The study was prematurely terminated by the sponsor due to enrollment challenges arising from a decreased medical need for pegcetacoplan in CAD. Due to the premature termination of the study, a part of the planned assessments and analyses were not performed as the number of patients available for many of the analyses renders them futile. The subgroup analyses were confined to primary and key secondary endpoints; duration of response was removed from the analysis; normalization of markers of hemolysis was not assessed beyond Week 24. No Week 96 evaluations were performed; the last available assessment during the treatment period was at Week 88 and the 8-week post-treatment follow-up.

The primary efficacy endpoint of the study was the response to treatment at Week 24 based on Hb levels at Week 16, maintenance of this effect from Week 16 to Week 24, and the absence of PRBC transfusions. Likely due to the smaller than planned sample size due to early termination of the study, and also to the higher than anticipated response rate in placebo, the primary endpoint of the study was not met.

The key secondary efficacy endpoints of the study were the change from Baseline to Week 24 in Hb level, transfusion avoidance from Week 5 to Week 24, and change from Baseline to Week 24 in the FACT-An score. Formal statistical testing could not be performed for key secondary endpoints according to the hierarchical testing strategy as the primary endpoint was not met. However, the mean changes from Baseline in Hb levels indicate that pegcetacoplan showed a numerically better treatment response that would have been statistically significant if formally tested compared to placebo.

Minimal changes from Baseline in the hemolytic markers, safety laboratory markers, FACIT-F subscore, SF-12, EQ-5D-5L scores were observed.

All patients receiving pegcetacoplan showed measurable drug concentrations from Week 1 to EOT/ET visits. Overall, pegcetacoplan trough concentrations were in-line with observations from previous studies where the same dosing regimen was applied.

Overall, pegcetacoplan showed a consistent effect on complement C3 levels and some effect in the alternative complement pathway activity.

Overall, pegcetacoplan treatment was associated with a slightly higher incidence of TEAEs, including TESAEs, compared with placebo. Majority of those TEAEs were of mild severity. No clinically meaningful changes were observed in the clinical chemistry, coagulation, and urinalysis assessments.

There were no safety concerns from vital signs or ECG findings.

13.2. Overall conclusions

Mean changes from baseline in Hb levels and other markers of hemolysis suggest that patients treated with pegcetacoplan exhibited a better treatment response compared to placebo. However, since the primary and key secondary efficacy endpoints of this study were not met, no firm conclusions on the efficacy of pegcetacoplan in patients with CAD can be drawn. The small sample size due to the early termination of the study, particularly in the placebo group, made comparisons between pegcetacoplan and placebo difficult. However, based on mean changes from baseline in Hb levels and other markers of hemolysis, patients treated with pegcetacoplan exhibited a better treatment response compared to placebo.

The safety findings observed with pegcetacoplan in this study are in agreement with the established safety profile and anticipated safety outcomes within the CAD population, specifically in elderly patients with frequent concomitant conditions such as the study population and the general population with CAD.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INLCUDED IN THE TEXT

14.1. Demographic Data

14.2. Efficacy and Pharmacokinetic/Pharmacodynamic Data

14.2.1. Efficacy Data

14.2.2. Pharmacokinetic/Pharmacodynamic Data

14.3. Safety Data

14.3.1. Displays of Adverse Events

14.3.2. Listings of Deaths, Other Serious and Significant Events, and Adverse Events Leading to Treatment Discontinuation

Listing of deaths, SAEs, and other significant events, and adverse events leading to treatment discontinuation is provided in Appendix 16.2.7 (Listing 16.2.7). No separate listings for deaths, SAEs or significant events, or events to leading to treatment discontinuation were generated.

14.3.3. Narratives of Deaths, Other Serious, and Certain Other Significant Adverse Events, and Adverse Events Leading to Treatment Discontinuation

Narrative for Patient 320301

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Event (SAE)
Study medication:	Parts A and B – Pegcetacoplan
Date of first dose:	04 Dec 2023 (Study Day 1)
Date of last dose:	01 Jul 2024 (Study Day 211)
Event preferred term (verbatim term):	Enterococcal sepsis (Sepsis with documented bactiremia with E. faecalis from digestive origin)
Start/stop dates:	08 Jan 2024 (Study Day 36) / 17 Jan 2024 (Study Day 45)
Action taken with the IMP:	Not applicable
Intensity:	Severe
Relationship per investigator:	Not related
Relationship per sponsor:	Not related
Outcome:	Recovered/Resolved
Led to study withdrawal:	No

Patient 320301 was a 77-year-old White, not Hispanic or Latino female, who was diagnosed with CAD on 24 Apr 2006. Relevant medical history included Large intestinal polyp (verbatim: colon polyps; 2009 to 2019) and Aortic aneurysm repair (verbatim: abdominal aortic aneurism – surgery; on 30 Jun 2022). Ongoing conditions included Hypothyroidism (since Feb 2004); Hypercholesterolaemia and Chronic obstructive pulmonary disease (verbatim: chronic obstructive bronchopneumpathy) (both since 2013); Arteritis (verbatim: legs arteritis, since 2018), Atrial fibrillation (verbatim: paroxysmal atrial fibrillation; since Dec 2020); Ageusia (verbatim: taste lost [COVID]), Anosmia, and Hypertension (verbatim: arterial hypertension) (all since 2021); Chronic kidney disease (verbatim: chronic kidney insufficiency; since 2022), Cold type haemolytic anaemia (verbatim: anemia gr2 related to CAD; since 28 Sep 2023); lacrimation increased (watering eyes gr1) and Dyspnoea (dyspnea gr2 [related to anemia]) (both since 01 Oct 2023); Constipation (verbatim: chronic constipation gr1, Fatigue (verbatim: faitigue gr1), Arthralgia (verbatim: rheumatic pain [right shoulder] gr1), and Pruritus (verbatim: prurit gr1) (all since 23 Oct 2023). The patient was randomly assigned to receive pegcetacoplan 1080 mg twice weekly and received the first dose of the IMP in the double-blind treatment period (Part A) on 04 Dec 2023 (Study Day 1).

On 23 Dec 2023 (Study Day 20), the patient experienced a non-SAE of Bronchitis (verbatim: bronchial infection) of moderate severity. On 08 Jan 2024 (Study Day 36), the patient experienced abdominal pain with cramps, nausea, constipation, and received oral macrogol 3350/potassium chloride/sodium bicarbonate/sodium chloride 1 dose (exact dose was not specified) TID. The patient had diarrhea after taking this medication. On the same day (08 Jan 2024), an SAE of Enterococcal sepsis (verbatim: sepsis with documented bactiremia E. faecalis from digestive origin) of severe intensity was reported. The event met the seriousness criteria of hospitalization. On this day (08 Jan 2024), a non-SAE of Bacteriuria (verbatim: asymptomatic bacteriuria [E. coli])

of moderate severity was reported. On 09 Jan 2024 (Study Day 36), the patient received oral metoclopramide hydrochloride 10 mg once and oral otilonium bromide 40 mg QD. On 11 Jan 2024 (Study Day 39), the patient's abdominal pain decreased, but diarrhea continued. On 12 Jan 2024 (Study Day 40), the patient was presented to the emergency with the complaints of orthostatic syncope due to dehydration caused by profuse diarrhea with inflammatory syndrome and malaise. Relevant laboratory investigations showed high levels of neutrophils at 17.79 × 10^3 cells/mm^3 (reference range: 2.0 to 7.7 × 10^3 cells/mm^3), WBC count at 19.1 × 10^3 cells/mm^3 (reference range: 4.0 to 11.0 × 10^3 cells/mm^3), and CRP at 148 mg/L (reference range: 0 to 5 mg/L); low levels of lymphocytes at 0.36 × 10^3 cells/mm^3 (reference range: 0.8 to 4.0 × 10^3 cells/mm^3) and sodium at 129 mmol/L (reference range: 136 to 145 mmol/L). An aerobic blood culture showed *Enterococcus faecalis* with a high level of resistance to streptomycin and *Escherichia coli*. A urine culture showed *E. coli*. On 16 Jan 2024 (Study Day 44), follow-up tests showed that the patient's neutrophil, lymphocyte, and sodium levels returned to normal; CRP level improved, but remained elevated at 16 mg/L (reference range: 0 to 5 mg/L). Treatment received during hospitalization included IV hydration, IV amoxicillin sodium/clavulanate potassium 1g QID (12 Jan 2024 to 17 Jan 2024); SC nadroparin calcium 0.3 mL QD as prophylaxis and inhalation tiotropium bromide monohydrate 2 doses QD (both from 13 Jan 2024 to 17 Jan 2024); inhalation ipratropium bromide 0.25 mg QID (13 Jan 2024 to 16 Jan 2024), and oral amoxicillin sodium/clavulanate potassium 875 mg TID (17 Jan 2024 to 19 Jan 2024). The SAE of Enterococcal sepsis and non-SAE of Bacteriuria were resolved by 17 Jan 2024 (Study Day 45), and the patient was discharged from the hospital on the same day (17 Jan 2024). The non-SAE of Bronchitis was resolved by 26 Jan 2024 (Study Day 54). The action taken with the IMP due to the SAE of Enterococcal sepsis was reported as not applicable. The investigator considered the SAE of Enterococcal sepsis as not related to the IMP and device. The sponsor assessed the SAE of Enterococcal sepsis to be not related to the IMP. It was attributed to the patient's elderly age and the underlying chronic pathologies (Chronic obstructive pulmonary disease and Chronic kidney disease), and Large intestine polyp were considered to be the risk factors. The large intestine polyps were not present since 2019, hence the risk factor should be read as possible presence of large intestine polyps that might have been recurred after 2019 as known to occur in some cases.

On 27 May 2024 (Study Day 176), the patient completed Part A and received the first dose of pegcetacoplan in the open-label treatment period (Part B). The IMP was withdrawn due to the sponsor decision, with the last dose received during Part B on 01 Jul 2024 (Study Day 211).

Concomitant medications taken within 30 days of the SAE of Enterococcal sepsis included oral levothyroxine 100 µg QD (since Feb 2004), oral folic acid 4 mg QD (since Mar 2006); oral fenoterol hydrobromide/ipratropium bromide 1 puff as needed and oral pravastatin sodium 20 mg QD (both since 2013); oral bisoprolol fumarate 2.5 mg QD and oral colecalciferol 1 ampule every month (both since 2020); oral apixaban 5 mg BID and oral flecainide acetate 150 mg QD (both since Dec 2020); oral losartan potassium 50 mg QD (since 2022), oral furosemide 40 mg QD (since 08 Feb 2022), inhalation tiotropium bromide monohydrate 2 doses BID (since 25 May 2022), oral paracetamol 1 g as needed (since 02 Jul 2022), oral ipratropium bromide/salbutamol sulfate 1 puff (unknown frequency; since 03 Nov 2023), inhalation ipratropium bromide/salbutamol sulfate 1 dose as needed (since 04 Dec 2023); inhalation fenoterol hydrobromide/ipratropium bromide 1 puff as needed, inhalation fluticasone furoate/umeclidinium bromide/vilanterol trifenatate 1 dose QD, and inhalation ipratropium bromide/salbutamol sulfate 1 dose TID (all since 23 Dec 2023); oral amoxicillin 1 g TID (23 Dec 2023 to 29 Dec 2023); oral azithromycin 250 mg QD (since 29 Dec 2023 and 31 Dec 2023 to 03 Jan 2024); intramuscular (IM) meningococcal vaccine B

RFHBP/NADA/NHBA OMV 1 dose once and IV ferric carboxymaltose 500 mg once (both on 03 Jan 2024).

During the study, the patient experienced other non-SAEs of Cold type haemolytic anaemia (verbatim: worsening of ongoing CAD; started on 04 Dec 2023, the day of the first dose of the IMP), Gastrooesophageal haemorrhage, Haemangioma (verbatim: digestive angioma), and Oesophagitis.

The patient did not complete the study as per the protocol due to the sponsor decision, with the last visit reported on 02 Sep 2024 (Study Day 274).

Narrative for Patient 340101

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Event (SAE)
Study medication:	Parts A, B, and C - Pegcetacoplan
Date of first dose:	13 Feb 2023 (Study Day 1)
Date of last dose:	04 Jul 2024 (Study Day 508)
Event preferred term (verbatim term):	Cold type haemolytic anaemia (cold agglutinin disease worsening)
Start/stop dates:	29 Jul 2024 (Study Day 533) / Ongoing
Action taken with the IMP:	Not applicable
Intensity:	Severe
Relationship per investigator:	Not related
Relationship per sponsor:	Not related
Outcome:	Not recovered/Not resolved
Led to study withdrawal:	No

Patient 340101 was a 64-year-old White, not Hispanic or Latino female, who was diagnosed with CAD in Jun 2015. Relevant medical history included Rheumatoid arthritis (1977 to 1979) and COVID-19 pneumonia (verbatim: COVID-19 bilateral pneumonia) × 2 events (in Mar 2020 and Jan 2022). Ongoing conditions included Bundle branch block right (verbatim: right bundle branch block of His bundle G1; start date was not provided), Raynaud's phenomenon (verbatim: Raynaud's phenomenon G2; since Jun 2015), and Asthenia (verbatim: Asthenia G1; since 15 Feb 2022). The patient was randomly assigned to receive pegcetacoplan 1080 mg twice weekly and received the first dose of IMP in the double-blind treatment period (Part A) on 13 Feb 2023 (Study Day 1).

On 01 Aug 2023 (Study Day 170), the patient completed Part A and received the first dose of the IMP in the open-label treatment period (Part B). On 13 Jan 2024 (Study Day 335), the patient completed Part B and received the first dose of the IMP in the open-label maintenance period (Part C). On 16 Jan 2024 (Study Day 338), a non-SAE of Cold type haemolytic anaemia (verbatim: worsening of cold agglutinin disease anemia) of mild severity was reported. Treatment included oral cyanocobalamin/folic acid 1 tablet QD (16 Jan 2024 to 29 Jul 2024). The non-SAE of Cold type haemolytic anaemia was resolved by 25 Apr 2024 (Study Day 438). The IMP was withdrawn

due to the sponsor decision, with the last dose received during Part C on 04 Jul 2024 (Study Day 508).

On 29 Jul 2024 (Study Day 533; 25 days after the last dose of the IMP), the patient promptly visited the research site with the complaints of progressive asthenia up on minimal exertion and jaundice. Erythrocyte morphology showed the presence of spherocytosis and cryoagglutinins; direct Coombs test was positive for complement (unspecified); serum monoclonal component was 1.56 g/L, vitamin B12 was 242 pg/mL (reference ranges were not provided), and serum immunofixation for IgMK was positive. Irregular antibodies with a thermal range of 30°C were found. The abnormal laboratory test results included low Hb at 65 g/L (reference range: 120 to 150 g/L) and high bilirubin at 2.0 mg/dL (reference range: <0.6 mg/dL), while the reticulocyte count, creatinine, and LDH levels were normal. These laboratory tests confirmed severe anemia with mild hemolysis and deficiency of maturation factors. On the same day (29 Jul 2024), the patient was diagnosed with an SAE of Cold type haemolytic anaemia (verbatim: cold agglutinin disease worsening) of severe intensity. The event met the seriousness criteria of an important medical event. Treatment included oral folic acid 10 mg QD (from 29 Jul 2024 onwards) and IM cyanocobalamin 1000 µg QD (29 Jul 2024 to 01 Aug 2024) with the frequency changed to every week (from 01 Aug 2024 to 29 Aug 2024). The patient was also transfused with 2 units of warm hematite concentrates. Post-transfusion, the Hb levels improved but remained low at 85 g/L (reference range: 120 to 150 g/L). The patient left the research site with a slight improvement in asthenia. A follow-up on 05 Aug 2024 (Study Day 540) revealed persistently low Hb level at 91 g/L (reference range: 120 to 150 g/L), whereas the reticulocyte count was high at 270×10^9 cells/L (reference range: 25 to 90×10^9 cells/L) and total bilirubin was elevated at 2.0 mg/dL (reference range: <0.6 mg/dL). The patient's haptoglobin was <0.01 g/L, indirect bilirubin was 1.3 mg/dL, and ferritin was 1063 ng/mL with soluble transferrin receptor of 2.9 mg/L (reference ranges were not provided). The LDH level was normal. It was reported that the patient's anemia was stable after transfusion but had moderate asthenia. Iron deficiency was confirmed, which was treated with oral ferrous sulfate 325 mg QD (05 Aug 2024 to 19 Aug 2024) and oral ferrimannitol ovalbumin 80 mg (frequency was reported as unknown; from 19 Aug 2024 onwards). On 29 Aug 2024 (Study Day 564), the Hb level was low at 93 g/L (reference range 120 to 150 g/L), while the reticulocyte count was high at 169×10^9 cells/L (reference range: 25 to 90×10^9 cells/L). The abnormal laboratory parameters included elevated levels of total bilirubin at 35.9 µmol/L (reference range: 5.1 to 20.5 µmol/L), direct bilirubin at 13.0 µmol/L (reference range: 0 to 5.1 µmol/L), ferritin at 3217 pmol/L (reference range: 22 to 640 pmol/L), indirect bilirubin at 22.9 µmol/L (reference range: 0 to 20.5 µmol/L), and vitamin B12 at 1059 pmol/L (reference range: 156 to 672 pmol/L), whereas haptoglobin was low at <0.2 g/L (reference range: 0.4 to 2.4 g/L). The frequency of IM cyanocobalamin 1000 µg was changed to every month (from 29 Aug 2024 onwards). The action taken with the IMP due to the SAE of Cold type haemolytic anaemia was reported as not applicable. The investigator considered the SAE of Cold type haemolytic anaemia as not related to the IMP and device. The sponsor assessed the SAE of Cold type haemolytic anaemia to be not related to the IMP but listed the progressive nature of the underlying primary CAD as a contributory risk factor.

Concomitant medications taken within 30 days of the SAE of Cold type haemolytic anaemia included oral zolpidem 10 mg QD (start date was reported as unknown) and oral ebastine 10 mg as needed (since 22 Nov 2023).

During the study, the patient experienced other non-SAEs of Upper respiratory tract infection × 2 events, Arthralgia, Pruritus (verbatim: pruritus, capillary pruritus, back pruritus, and generalized pruritus), and Shoulder girdle pain.

The patient did not complete the study as per the protocol due to the sponsor's decision, with the last visit reported on 29 Aug 2024 (Study Day 564). The SAE of Cold type haemolytic anaemia was reported as not resolved at the time of study discontinuation.

Narrative for Patient 430102

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Events (SAEs)
Study medication:	Parts A, B, and C - Pegcetacoplan
Date of first dose:	20 Oct 2022 (Study Day 1)
Date of last dose:	08 Jul 2024 (Study Day 628)
Event preferred term (verbatim term):	1) Autoimmune haemolytic anaemia (mixed autoimmune haemolytic anaemia) 2) Autoimmune haemolytic anaemia (mixed autoimmune haemolytic anaemia)
Start/stop dates:	1) 24 Jul 2024 (Study Day 644) / 25 Jul 2024 (Study Day 645) 2) 26 Jul 2024 (Study Day 646) / 02 Aug 2024 (Study Day 653)
Action taken with the IMP:	Both events: Not applicable
Intensity:	Both events: Moderate
Relationship per investigator:	Both events: Not related
Relationship per sponsor:	Both events: Not related
Outcome:	Both events: Recovered/Resolved
Led to study withdrawal:	Both events: No

Patient 430102 was an 83-year-old White, not Hispanic or Latino female, who was diagnosed with CAD on 01 Jan 2006. No relevant medical history was reported. Ongoing conditions included Back pain and Osteoporosis (start dates were not provided) and Diaphragmatic hernia (since 2017). The patient was randomly assigned to receive pegcetacoplan 1080 mg twice weekly and received the first dose of the IMP in the double-blind treatment period (Part A) on 20 Oct 2022 (Study Day 1).

On 06 Apr 2023 (Study Day 169), the patient completed Part A and received the first dose of the IMP in the open-label treatment period (Part B). On 21 Sep 2023 (Study Day 337), the patient completed Part B and received the first dose of the IMP in the open-label maintenance period (Part C). The IMP was withdrawn due to the premature termination of the study by the sponsor, with the last dose received during Part C on 08 Jul 2024 (Study Day 628).

On 11 Jul 2024 (Study Day 631; 3 days after the last dose of the IMP), the patient had low levels of Hb at 89 g/L (reference range: 120 to 160 g/L), erythrocytes at 2.7×10^{12} cells/L (reference range: 3.8 to 5.2×10^{12} cells/L), hematocrit at 25.8% (reference range: 35 to 47%), and haptoglobin at <0.2 g/L (reference range: 0.4 to 2.4 g/L. The patient had normal levels of AST at 22 U/L

(reference range 14 to 34 U/L) and LDH isoenzyme 1 at 195 U/L (reference range 120 to 246 U/L), while blood urea nitrogen was high at 8.5 mmol/L (reference range: 3.2 to 8.2 mmol/L). Since mid Jul 2024, the patient experienced increasing fatigue. On 23 Jul 2024 (Study Day 643), the patient felt weakness, tiredness, and noticed having dark brown urine. On 24 Jul 2024 (Study Day 644; 16 days after the last dose of the IMP), the patient visited the hospital and underwent laboratory tests, which revealed low Hb at 7.4 g/dL, high total bilirubin at 4.17 mg/dL, and LDH at 976 U/L (reference ranges were not provided); a Coombs test showed positive results for Anti IgG, anti C3c, and anti C3d antibodies (no quantitative results were reported in the CIOMS). On the same day (24 Jul 2024), the patient was diagnosed with an SAE of Autoimmune haemolytic anaemia (verbatim: mixed autoimmune haemolytic anaemia) of moderate severity and was subsequently hospitalized. The event met the seriousness criteria of hospitalization. Additionally, a non-SAE of Warm autoimmune haemolytic anaemia (WAIHA [warm antibody autoimmune hemolytic anaemia]) of moderate severity was reported on this day (24 Jul 2024). It was reported that the patient's hemolytic anaemia was due to both cold and warm agglutinins. On the same day (24 Jul 2024), the patient received 2 units of PRBC transfusions and IV sutimlimab 6500 mg once. The SAE of Autoimmune haemolytic anaemia was resolved by 25 Jul 2024 (Study Day 645), and the patient was discharged from the hospital on the same day (25 Jul 2024) in an improved condition. The action taken with the IMP due to the SAE of Autoimmune haemolytic anaemia was reported as not applicable. The investigator considered the SAE of Autoimmune haemolytic anaemia as not related to the IMP and device.

On 26 Jul 2024 (Study Day 646; 18 days after the last dose of the IMP), the patient was advised to visit the hospital for follow-up blood tests, which revealed persistent anemia with a low Hb level of 6.9 g/dL (reference range: 12.0 to 16.0 g/dL) and a low RBC count of 2.4×10^3 cells/L (reference range: 3.8 to 5.2×10^3 cells/L). Additionally, the patient's COVID-19 test result was positive. On the same day (26 Jul 2024), the patient was diagnosed with a second SAE of Autoimmune haemolytic anaemia (verbatim: mixed autoimmune haemolytic anaemia) of moderate severity and was hospitalized for further evaluation. The event met the seriousness criteria of hospitalization. On this day (26 Jul 2024), the patient received 2 units of PRBC transfusions. During hospitalization, the non-SAEs of COVID-19 (verbatim: SARS-COV-2-infection; moderate severity) and Urinary tract infection (verbatim: infection – nitrit positive urine), both of moderate severity (on 26 Jul 2024 [Study Day 646]); Vertigo (verbatim: vertigo), Diplopia (verbatim: double vision), Aphasia (verbatim: amnesic dysphasia), and Slow response to stimuli (verbatim: slow down reaction [according patient]), all of mild severity (on 29 Jul 2024 [Study Day 649]) were reported. On 29 Jul 2024 (Study Day 649), a magnetic resonance tomography (anatomical location not specified) result was normal. The non-SAEs of Vertigo and Diplopia were resolved by 01 Aug 2024 (Study Day 652). On 02 Aug 2024 (Study Day 653), the patient had low levels of Hb at 8.6 g/dL (reference range: 12.0 to 16.0 g/dL), erythrocyte count at 2.9×10^3 cells/L (reference range: 3.8 to 5.2×10^3 cells/L), hematocrit at 28.2% (reference range: 35.0 to 47.0%), and haptoglobin at 12.7 mg/dL (reference range: 30 to 200 mg/dL); high levels of absolute reticulocyte count at 116.8 g/L (reference range: 32.0 to 110.0 g/L) and glucose at 127 mg/dL (reference range: 74 to 109 mg/dL); LDH was 300 IU/L (reference range was not provided). A urine-nitrite test result was positive (date was not specified). During hospitalization, the patient was treated with IV fosfomycin 3 g once (on 26 Jul 2024), oral nirmatrelvir/ritonavir 1 tablet BID (26 Jul 2024 to 30 Jul 2024), and IV methylprednisolone 64 mg QD (28 Jul 2024 to 29 Jul 2024). The SAE of Autoimmune haemolytic anaemia (second event) and the non-SAEs of Warm autoimmune haemolytic anaemia, COVID-19, Urinary tract infection, Aphasia, and Slow

response to stimuli were resolved by 02 Aug 2024 (Study Day 653). On 03 Aug 2024 (Study Day 654), the patient was discharged from the hospital in an improved general condition. The patient received IV sutimlimab 6.5 g once (on 13 Aug 2024). The action taken with the IMP due to the SAE of Autoimmune haemolytic anaemia (second event) was reported as not applicable. The investigator considered the SAE of Autoimmune haemolytic anaemia (second event) as not related to the IMP and device.

The sponsor assessed the SAEs of Autoimmune haemolytic anaemia (both events) to be not related to the IMP. It was reported that CAD and non-SAEs of Warm autoimmune haemolytic anaemia along with COVID-19 triggered the SAEs of Autoimmune haemolytic anaemia (both events).

Concomitant medications taken within 30 days of the SAE of Autoimmune haemolytic anaemia (×2 events) included oral gingko biloba extract 80 mg QD (since 01 Jan 2000), oral tramadol hydrochloride 150 mg as needed (since 01 Jul 2022), oral dexibuprofen 200 mg BID (since 11 Oct 2022); oral bisacodyl 5 mg QD and oral macrogol 3350/potassium chloride/sodium bicarbonate/sodium chloride 13.8 g QD (both since 05 Jan 2023).

During the study, the patient experienced other non-SAE of Injection site swelling, Fatigue, Constipation, and Abdominal pain (× 2 events).

The patient did not complete the study as per the protocol due to the premature termination of the study by the sponsor, with the last visit reported on 03 Sep 2024 (Study Day 685).

Narrative for Patient 430103

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Events (SAEs) and Treatment Discontinuation due to an Adverse Event (AE)
Study medication:	Parts A, B, and C - Pegcetacoplan
Date of first dose:	08 Nov 2022 (Study Day 1)
Date of last dose:	31 Oct 2023 (Study Day 358)
Event preferred term (verbatim term):	1. Acute kidney injury (acute renal failure) 2. Cardiac failure (cardiac decompensation) 3. Cold type haemolytic anaemia (worsening of CAD anaemia) 4. Cold type haemolytic anaemia (symptomatic CAD anaemia) 5. Pneumonia (pneumonia [left])
Start/stop dates:	1. 20 Aug 2023 (Study Day 286) / 24 Aug 2023 (Study Day 290) 2. 26 Aug 2023 (Study Day 292) / 12 Sep 2023 (Study Day 309) 3. 23 Oct 2023 (Study Day 350) / 31 Oct 2023 (Study Day 358) 4. 11 Nov 2023 (Study Day 369) / 28 Nov 2023 (Study Day 386) 5. 28 Dec 2023 (Study Day 416) / 07 Jan 2024 (Study Day 426)
Action taken with the IMP:	Events 1 – 3: Not applicable Events 4 and 5: Drug withdrawn
Intensity:	Events 1 – 5: Moderate
Relationship per investigator:	Events 1 – 5: Not related

Relationship per sponsor:	Events 1 – 5: Not related
Outcome:	Events 1 – 5: Recovered/Resolved
Led to study withdrawal:	No

Patient 430103 was an 83-year-old White, not Hispanic or Latino male, who was diagnosed with CAD on 01 Apr 2019. No relevant medical history was reported. Ongoing conditions included Hyperuricaemia (since 1989), Hypertension (since 1992), Atrial fibrillation (since 2013); Cardiac failure and Hypothyroidism (both since 2019); and Renal failure (verbatim: renal insufficiency; since 2021). The patient was randomly assigned to receive pegcetacoplan 1080 mg twice weekly and received the first dose of IMP in the double-blind treatment period (Part A) on 08 Nov 2022 (Study Day 1).

On 14 Dec 2022 (Study Day 37), a non-SAE of Oedema peripheral (verbatim: bilateral leg oedema) of mild severity was reported, which was treated with oral spironolactone 25 mg QD (12 Jun 2023 to 20 Aug 2023). On 26 Apr 2023 (Study Day 170), the patient completed Part A and received the first dose of the IMP in the open-label treatment period (Part B).

On 01 Aug 2023 (Study Day 267), a non-SAE of Performance status decreased (verbatim: reduced performance status) of moderate severity was reported. On 07 Aug 2023 (Study Day 273), a non-SAE of Benign prostatic hyperplasia (verbatim: benign prostatic hypertrophy) of moderate severity was reported, which was treated with oral dutasteride/tamsulosin hydrochloride 0.5/0.4 mg QD (from 2023 onwards) and oral tamsulosin 0.4 mg every week (from 07 Aug 2023 onwards). On 11 Aug 2023 (Study Day 277), a non-SAE of Cold type haemolytic anaemia (verbatim: worsening of CAD anaemia) of moderate severity was reported, which was treated with SC epoetin theta 30,000 IU every week (12 Aug 2023 to 18 Aug 2023) with dose increased to 40,000 IU every week (18 Aug 2023 to 25 Oct 2023).

On 20 Aug 2023 (Study Day 286), the patient was presented to the hospital with the general feeling of illness (reduced performance status) and was subsequently admitted for further evaluation and treatment. The laboratory test results showed high levels of creatinine at 2.3 mg/dL (0.7 to 1.20 mg/dL), potassium at 6.48 mmol/L (reference range: 3.5 to 5.1 mmol/L), and blood urea nitrogen at 77.8 mg/dL (reference range: 8 to 23 mg/dL); low levels of glomerular filtration rate (GFR; MDRD-IDMS) at 27.09 mL/min/1.73 m^2 (reference range: >55 mL/min/1.73 m^2) and sodium at 134 mmol/L (reference range: 136 to 145 mmol/L). The patient had acidosis with a pH of 7.24, and hemolysis index was 6 (units and reference ranges were not provided). On the same day (20 Aug 2023), the patient was diagnosed with an SAE of Acute kidney injury (verbatim: acute renal failure) of moderate severity. The event met the seriousness criteria of hospitalization and an important medical event. Treatment included oral sodium zirconium cyclosilicate 10 mg as needed (20 Aug 2023 to 23 Aug 2023), oral sodium bicarbonate 840 mg TID (from 21 Aug 2023 onwards), and oral carvedilol 12.5 mg QD (21 Aug 2023 to 25 Oct 2023). The patient also underwent fluid substitution, which eventually led to the rapid improvement of the overall condition. The SAE of Acute kidney injury and non-SAE of Performance status decreased were resolved by 24 Aug 2023 (Study Day 290). The patient was discharged from the hospital in a good condition on the same day (24 Aug 2023). The action taken with the IMP due to the SAE of Acute kidney injury was reported as not applicable. The investigator considered the SAE of Acute kidney injury as not related to the IMP and device. The sponsor assessed the SAE of Acute kidney injury to be not related to the IMP. The underlying historical conditions of Hypertension and Renal failure as well as the concomitant medications (unspecified) were reported as contributing risk factors.

On 26 Aug 2023 (Study Day 292), the patient's pre-existing condition of Cardiac failure (verbatim: myocardial failure) worsened, causing symptoms of severe leg edema and pleural effusion. On the same day (26 Aug 2023), the patient was hospitalized with the diagnosis of an SAE of Cardiac failure (verbatim: cardiac decompensation) of moderate severity. The event met the seriousness criteria of hospitalization and an important medical event. No treatment was reported for this SAE; however, during the hospital stay, the patient received oral atorvastatin 40 mg QD (from 05 Sep 2023 onwards) as prophylaxis, oral bisoprolol 2.5 mg QD (05 Sep 2023 to 24 Oct 2023); oral febuxostat 80 mg QD, oral furosemide 90 mg QD, and oral spironolactone 25 mg QD (all from 05 Sep 2023 to 25 Oct 2023). On 08 Sep 2023 (Study Day 305), a non-SAE of COVID-19 (SARS-COV-2 infection) of mild severity was reported. The SAE of Cardiac failure and non-SAE of COVID-19 were resolved by 12 Sep 2023 (Study Day 309), and the patient was discharged from the hospital on the same day (12 Sep 2023) in a stable condition. The action taken with the IMP due to the SAE of Cardiac failure was reported as not applicable. The investigator considered the SAE of Cardiac failure as not related to the IMP and device. The sponsor assessed the SAE of Cardiac failure to be not related to the IMP but considered to be due to the underlying historical conditions of Atrial fibrillation and Cardiac failure (verbatim: myocardial failure).

On 10 Oct 2023 (Study Day 337), the patient completed Part B and received the first dose of the IMP in the open-label maintenance period (Part C). On this day (10 Oct 2023), the patient had low levels of Hb at 74 g/L (reference range: 135 to 180 g/L), hematocrit at 22.6% (reference range: 40 to 52%), and reticulocytes at 25.9×10^9 cells/L (reference range: 32 to 110×10^9 cells/L). On 23 Oct 2023 (Study Day 350), the patient was presented with a 3-week history of worsening weakness and fatigue. On the same day (23 Oct 2023), the non-SAE of Cold type haemolytic anaemia worsened (onset 11 Aug 2023), and the patient was diagnosed with an SAE of Cold type haemolytic anaemia (verbatim: worsening of CAD anaemia) of moderate severity and was subsequently hospitalized. The event met the seriousness criteria of hospitalization. The Hb level was 6.6 mg/dL (reference range was not provided). The patient received 2 units of PRBC transfusions. On an unspecified date during hospitalization, a gastroscopy was performed, which confirmed portal gastropathy. A fibroscan revealed cardiac cirrhosis (grade 4). This finding was reported as a non-SAE of Cardiac cirrhosis (verbatim: cirrhosis cardiaque) of moderate severity on 25 Oct 2023 (Study Day 352). Treatment also included oral carvedilol 12.5 mg QD and SC darbepoetin alfa 60 µg every week (both from 25 Oct 2023 onwards). The SAE of Cold type haemolytic anaemia was resolved by 31 Oct 2023 (Study Day 358). On the same day (31 Oct 2023), the patient was discharged from the hospital in a stable condition. The action taken with the IMP due to the SAE of Cold type haemolytic anaemia was reported as not applicable. The investigator considered the SAE of Cold type haemolytic anaemia as not related to the IMP and device. The sponsor assessed the SAE of Cold type haemolytic anaemia to be not related to the IMP but considered as related to the worsening of the underlying CAD.

On 11 Nov 2023 (Study Day 369), the patient was hospitalized with the symptoms of weakness and fatigue. At admission, the Hb level was 5.3 g/dL (reference range was not provided). On the same day (11 Nov 2023), the patient was diagnosed with an SAE of Cold type haemolytic anaemia (verbatim: symptomatic CAD anaemia) of moderate severity. The event met the seriousness criteria of hospitalization and an important medical event. The patient received 4 units of PRBC transfusions. The IMP was withdrawn due to the SAE of Cold type haemolytic anaemia (verbatim: symptomatic CAD anaemia), with the last dose received during Part C on 31 Oct 2023 (Study Day 358). On 20 Nov 2023 (Study Day 378), the patient started treatment with IV bendamustine/rituximab (dose and units were reported as unknown). The SAE of Cold type

haemolytic anaemia (verbatim: symptomatic CAD anaemia) was resolved by 28 Nov 2023 (Study Day 386), and the patient was discharged from the hospital on the same day (28 Nov 2023). The investigator considered the SAE of Cold type haemolytic anaemia (verbatim: symptomatic CAD anaemia) as not related to the IMP and device. The sponsor assessed the SAE of Cold type haemolytic anaemia (verbatim: symptomatic CAD anaemia) to be not related to the IMP but considered as related to the underlying primary CAD.

On 28 Dec 2023 (Study Day 416), the patient was presented with a 5-day history of slightly elevated body temperature (temperature recordings were not provided). A chest x-ray showed pneumonia in the left lower lobe of the lung. On the same day (28 Nov 2023), the patient was diagnosed with an SAE of Pneumonia (verbatim: pneumonia [left]) of moderate severity and was admitted to the hospital for therapy. The event met the seriousness criteria of hospitalization. Treatment included oral levofloxacin and IV piperacillin sodium/tazobactam sodium (dose and frequency were unknown; both from 28 Dec 2023 to 01 Jan 2024). On this day (28 Dec 2023), a non-SAE of Cold type haemolytic anaemia (verbatim: worsening of CAD anaemia) of moderate severity was reported. The patient received 4 units of PRBC transfusions. The SAE of Pneumonia was resolved by 07 Jan 2024 (Study Day 426), and the patient was discharged from the hospital on the same day (07 Jan 2024) in a stable condition. The action taken with the IMP due to the SAE of Pneumonia was reported as "drug withdrawn" by the investigator, while in the sponsor's assessment the action taken should have been "not applicable" as the drug had been already withdrawn due to the SAE of Cold type haemolytic anaemia (verbatim: symptomatic CAD anaemia; reported from 11 Nov 2023 to 28 Nov 2023), with the last dose of the IMP received on 31 Oct 2023. The investigator considered the SAE of Pneumonia as not related to the IMP and device. The sponsor assessed the SAE of Pneumonia to be not related to the IMP but listed the patient's elderly age and underlying chronic pathologies such as cardiac and renal failure as the confounding factors. In addition, the sponsor assessed that the patient had not received pegcetacoplan for 58 days before the onset of the event and considering the median product half-life of 8.6 days as per the EMA Summary of Product Characteristics, indicating that the circulating drug concentrations at the time of the event were likely low or negligible, further decreasing the likelihood of this effect to be drug-related.

Concomitant medications taken within 30 days of the SAEs of Acute kidney injury, Cardiac failure, Cold type haemolytic anaemia (×2 events; worsening of CAD anaemia and symptomatic CAD anaemia), and Pneumonia included oral ginkgo biloba extract 40 mg QD (since 2013), oral pantoprazole sodium sesquihydrate 40 mg QD (since 2020), oral dutasteride/tamsulosin hydrochloride 0.5/0.4 mg QD (since 2023), oral apixaban 2.5 mg BID (since 05 Mar 2023), oral dapagliflozin propanediol monohydrate 10 mg QD (since 01 Jun 2023), oral gabapentin 150 mg QD (since 01 Jul 2023), oral colecalciferol 40 drops every week (from 11 Aug 2023 onwards), and oral levothyroxine sodium 50 µg QD (since 19 Aug 2023). Concomitant medications taken within 30 days of the SAEs of Acute kidney injury and Cardiac failure included oral allopurinol 100 mg QD (1989 to 05 Sep 2023), oral bioflavonoids NOS/diosmin/hesperidin 500 mg QD (2002 to 20 Aug 2023); oral furosemide 40 mg QD and oral rosuvastatin 10 mg QD (both from 2019 to 20 Aug 2023); oral bisoprolol 2.5 mg QD (2020 to 20 Aug 2023), oral enalapril maleate 10 mg QD (16 Nov 2022 to 11 Aug 2023), and oral enalapril maleate/hydrochlorothiazide 20/12.5 mg QD (11 Aug 2023 to 20 Aug 2023). Concomitant medication taken within 30 days of the SAEs of Cold type haemolytic anaemia (×2 events; worsening of CAD anaemia and symptomatic CAD anaemia) and Pneumonia included oral eplerenone 25 mg QD (from an unknown date in Oct 2023 onwards). Concomitant medications taken within 30 days of the SAE Pneumonia included oral

allopurinol 100 mg QD, oral furosemide 40 mg BID, and oral potassium chloride 600 mg TID (all from an unknown date in Dec 2023 onwards).

During the study, the patient experienced other non-SAEs of Pruritus (verbatim: pruritus [back site] and pruritus [back]) and Headache.

The patient did not complete the study as per the protocol due to lack of efficacy, with the last visit reported on 10 Jan 2024 (Study Day 429). The non-SAE of Oedema peripheral was reported as resolving at the time of study discontinuation; the non-SAEs of Benign prostatic hyperplasia, Cardiac cirrhosis, and Cold type haemolytic anaemia (verbatim: worsening of CAD anaemia; onset 28 Dec 2023) were reported as not resolved at the time of study discontinuation.

Narrative for Patient 430104

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Event (SAE)
Study medication:	Part A – Placebo Part B – Pegcetacoplan Part C - Pegcetacoplan
Date of first dose:	26 Jan 2023 (Study Day 1)
Date of last dose:	08 Jul 2024 (Study Day 530)
Event preferred term (verbatim term):	Autoimmune haemolytic anaemia (mixed autoimmune haemolytic anaemia)
Start/stop dates:	31 Jul 2024 (Study Day 553) / 07 Aug 2024 (Study Day 560)
Action taken with the IMP:	Not applicable
Intensity:	Moderate
Relationship per investigator:	Not related
Relationship per sponsor:	Not related
Outcome:	Recovered/Resolved
Led to study withdrawal:	No

Patient 430104 was an 82-year-old White, not Hispanic or Latino female, who was diagnosed with CAD on 01 Jan 1997. No relevant medical history was reported. Ongoing conditions included Irritable bowel syndrome, Osteoporosis, Dyspnoea exertional, Atrial fibrillation, and Depression. The patient was randomly assigned to receive placebo 1080 mg twice weekly and received the first dose of the IMP in the double-blind treatment period (Part A) on 26 Jan 2023 (Study Day 1).

On 13 Jul 2023 (Study Day 169), the patient completed Part A and received the first dose of pegcetacoplan in the open-label treatment period (Part B). On 28 Dec 2023 (Study Day 337), the patient completed Part B and received the first dose of pegcetacoplan in the open-label maintenance period (Part C). The IMP was withdrawn due to the premature termination of the study by the sponsor, with the last dose received during Part C on 08 Jul 2024 (Study Day 530).

On 09 Jul 2024 (Study Day 531), the patient had low erythrocyte count of 3.6×10^{12} cells/µL (reference range: 3.8 to 5.2×10^{12} cells/µL), while Hb and hematocrit were normal. On an

unspecified date, the patient was presented to the emergency department with the complaints of increasing weakness and yellowish discoloration of the skin. Laboratory results showed low levels of Hb at 6.4 g/dL (reference range: 12 to 16 g/dL) and RBC count of 1.9 T/L (reference range: 3.8 to 5.2 T/L), while the total bilirubin and LDH levels were elevated, measuring 5.48 mg/dL (reference range: 0 to 1.2 mg/dL) and 516 U/L (reference range: <250 U/L), respectively. A Coombs test showed positive results for IgG. On 31 Jul 2024 (Study Day 553, 23 days after the last dose of the IMP), the patient was hospitalized with the diagnosis of an SAE of Autoimmune haemolytic anaemia (verbatim: mixed autoimmune haemolytic anaemia) of moderate severity. The event met the seriousness criteria of hospitalization. Treatment included 2 units of PRBCs (on 31 Jul 2024), SC darbepoetin alfa 15,000 U every week (from 01 Aug 2024 onwards) and IV rituximab 500 mg once (on 01 Aug 2024). The patient received IV diphenhydramine hydrochloride 60 mg and oral paracetamol 1000 mg before rituximab as prophylaxis (both from 01 Aug 2024 to 19 Aug 2024). On an unspecified date during hospitalization, the patient's Hb was 9.1 g/dL, total bilirubin was 2.34 mg/dL, and LDH at 501 U/L (reference ranges were not provided). Treatment included 2 units of PRBC transfusions (on 02 Aug 2024) and oral prednisolone 50 mg QD (06 Aug 2024 to 09 Aug 2024). The contributory and aggravating factor that led to the patient's Autoimmune haemolytic anaemia was the withdrawal of the IMP. The SAE of Autoimmune haemolytic anaemia resolved by 07 Aug 2024 (Study Day 560), and the patient was discharged from the hospital in a stable condition on the same day (07 Aug 2024). The patient received IV rituximab 499.98 mg once (on 12 Aug 2024) and SC rituximab 1400 mg once (on 19 Aug 2024). On 26 Aug 2024 (Study Day 579), the patient had low levels of Hb at 71 g/L (reference range: 120 to 160 g/L), erythrocytes at 2.3×10^{12} cells/µL (reference range: 3.8 to 5.2×10^{12} cells/µL), and hematocrit at 21.5% (reference range: 35 to 47%). The action taken with the IMP due to the SAE of Autoimmune haemolytic anaemia was reported as not applicable. The investigator considered the SAE of Autoimmune haemolytic anaemia as not related to the IMP and device. The sponsor assessed the SAE of Autoimmune haemolytic anaemia to be not related to the IMP. The underlying disease of CAD was determined to the be the contributory risk factor for the event.

Concomitant medications taken within 30 days of the SAE of Autoimmune haemolytic anaemia included oral bisoprolol fumarate 5 mg QD and oral edoxaban tosilate 60 mg QD (both since Dec 2021), oral quetiapine fumarate 25 mg QD (since 21 Dec 2022), oral escitalopram 10 mg QD (since 13 Jul 2023), oral furosemide 20 mg QD (since 04 Sep 2023), ophthalmic bimatoprost/timolol maleate 1 drop in left eye QD (since Apr 2024), and oral bupropion hydrochloride 150 mg QD (since Jun 2024).

During the study, the patient experienced non-SAEs of Oedema peripheral (verbatim: leg edema [both]), Influenza, and Gait disturbance (verbatim: unsteady gait).

The patient did not complete the study as per the protocol due to the premature termination of the study by the sponsor, with the last visit reported on 26 Aug 2024 (Study Day 579).

Narrative for Patient 440102

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Event (SAE) and Treatment Discontinuation due to an Adverse Event (AE)
Study medication:	Part A - Pegcetacoplan
Date of first dose:	21 Feb 2023 (Study Day 1)
Date of last dose:	25 Jul 2023 (Study Day 155)
Event preferred term (verbatim term):	Cholecystitis (Cholecystitis)
Start/stop dates:	28 Jul 2023 (Study Day 158) / 29 Jul 2023 (Study Day 159)
Action taken with the IMP:	Drug withdrawn
Intensity:	Severe
Relationship per investigator:	Not related
Relationship per sponsor:	Not related
Outcome:	Fatal
Led to study withdrawal:	Yes

Patient 440102 was an 84-year-old White, Hispanic or Latino female, who was diagnosed with CAD on 16 Feb 2017. Relevant medical history included Warm autoimmune haemolytic anaemia (unknown start date to Mar 2020). Ongoing conditions included Diverticulum, Hiatus hernia, Ocular icterus, Blood cholesterol increased, and Dizziness (no start dates were reported), Lymphoproliferative disorder (unknown start date to reported end date of 29 Jul 2023), Deafness (since 16 Feb 1991), Atrial fibrillation (since 2021, reported as not ongoing, but no end date available), Cyanosis (verbatim: acrocyanosis of feet and fingers; since 02 Nov 2021); Jaundice and Pallor (both since 24 Jan 2023).The patient was randomly assigned to receive pegcetacoplan 1080 mg twice weekly and received the first dose of the IMP in the double-blind treatment period (Part A) on 21 Feb 2023 (Study Day 1).

On 11 Jul 2023 (Study Day 141), the patient's relevant abnormal laboratory parameters included elevated levels of ALT at 41 U/L (reference range: 0 to 33 U/L), ALP at 108 U/L (reference range: 42 to 98 U/L), bilirubin at 53.4 µmol/L (reference range: 5.1 to 20.5 µmol/L), direct bilirubin at 18.3 µmol/L (reference range: 0 to 5.1 µmol/L), and indirect bilirubin at 35.1 µmol/L (reference range: 0 to 20.5 µmol/L). On 23 Jul 2023 (Study Day 153), the patient experienced a non-SAE of Abdominal pain (verbatim: abdominal pain) of mild severity, which was resolved by 25 Jul 2023 (Study Day 155). On 28 Jul 2023 (Study Day 158; 3 days after the last dose of the IMP), the patient was presented to the emergency department with severe abdominal pain and increased body temperature. The patient was treated with paracetamol (dose and frequency was not reported; from 28 Jul 2023 onwards). An abdomen and pelvis CT scan revealed findings consistent with acute cholecystitis with bilobar intra- and extra-hepatic biliary duct dilation. The common bile duct measured up to 1.2 cm at the porta hepatis. The assessment of pancreas was severely limited by motion artefact, where concurrent acute pancreatitis was not ruled out. A trace amount of free fluid extending from the tail of pancreas into the mesentery and left paracolic gutter was observed. On the same day (28 Jul 2023), the patient was diagnosed with an SAE of Cholecystitis (verbatim:

cholecystitis) of severe intensity. The event met the seriousness criteria of hospitalization, important medical event, and the event causing death. The patient's amylase was high at 4551 U/L (reference range: 30 to 110 U/L); Hb was 83, ALP was 130, ALT was 180, bilirubin was 170, WBC was 3.2, urea was 7.9, platelet count was 65, and neutrophil count was 1.3 (units and reference ranges were not provided). On 29 Jul 2023 (Study Day 159), the patient's abnormal laboratory parameters included elevated levels of bilirubin at 109 µmol/L (reference range: 0 to 21 µmol/L), creatinine at 124 µmol/L (reference range: 49 to 92 µmol/L), CRP at 74 mg/L (reference range: 0 to 5 mg/L); INR at 2.0 (reference range: 0.8 to 1.3), aPTT ratio at 2.2 (reference range: 0.8 to 1.2), prothrombin time at 67.3 seconds (reference range: 25 to 38 seconds), ALT at 821 IU/L (reference range: 0 to 33 IU/L), and urea 10.1 mmol/L (reference range: 2.9 to 8.2 mmol/L), while estimated glomerular filtration rate was low at 37 × 1.73 mL/min/m^2 (reference range: 90-9999 × 1.73 mL/min/m^2). The IMP was withdrawn during due to the SAE of Cholecystitis, with the last dose received during Part A on 25 Jul 2023 (Study Day 155). No treatment was given, and no surgery was performed due to the high risk and possible pancreatitis. The patient's condition deteriorated with reduced consciousness and developed sepsis and low blood pressure. On the same day (29 Jul 2023), the patient died due to the SAE of Cholecystitis, which resulted in the permanent discontinuation from the study. No autopsy was performed. The outcome of the SAE of Cholecystitis was reported as fatal. The investigator considered the SAE of Cholecystitis as not related to the IMP and device. The sponsor assessed the SAE of Cholecystitis to be not related to the IMP. The details on the course of the event, treatment, and circumstances leading to patient's death were missing.

Concomitant medications taken within 30 days of the SAE of Cholecystitis included oral vitamin D NOS 1000 µg QD (unknown start date), oral atorvastatin 20 mg QD (since 11 Jan 2019), oral folic acid 5 mg QD (since 15 Jul 2019), oral lansoprazole 30 mg QD (since 02 Sep 2021), oral apixaban 2.5 mg BID (since 20 Sep 2021), and oral prednisolone 10 mg QD (since Jan 2022).

During the study, the patient experienced other non-SAEs of Nausea, Fatigue, Blepharitis, Dizziness, and Oedema peripheral.

The patient did not complete the study as per the protocol due to the SAE of Cholecystitis that led to the patient's death, with the last visit reported on 29 Jul 2023 (Study Day 159).

Narrative for Patient 440103

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Events (SAEs) and Treatment Discontinuation due to an Adverse Event (AE)
Study medication:	Part A - Pegcetacoplan
Date of first dose:	28 Feb 2023 (Study Day 1)
Date of last dose:	03 Apr 2023 (Study Day 35)
Event preferred term (verbatim term):	1. Haemolytic anaemia (severe anaemia [worsening of haemolytic anaemia]) 2. Pneumonia (hospital acquired pneumonia)
Start/stop dates:	1. 06 Apr 2023 (Study Day 38) / 28 Apr 2023 (Study Day 60) 2. 08 May 2023 (Study Day 70) / 26 May 2023 (Study Day 88)

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Events (SAEs) and Treatment Discontinuation due to an Adverse Event (AE)
Action taken with the IMP:	1. Drug withdrawn 2. Not applicable
Intensity:	Events 1 and 2: Severe
Relationship per investigator:	Events 1 and 2: Not related
Relationship per sponsor:	Events 1 and 2: Not related
Outcome:	Events 1 and 2: Recovered/Resolved
Led to study withdrawal:	Combination of the SAE Haemolytic anaemia and multiple non-SAEs

Patient 440103 was a 70-year-old White, not Hispanic or Latino male, who was diagnosed with CAD on 01 Jul 2019. No medical history was reported for this patient. Ongoing conditions included Cyanosis (start date was not reported), B-cell lymphoma (CD5 positive small B cell lymphoma; since Oct 2019); Cryoglobulinaemia and Raynaud's phenomenon (both since 11 Nov 2019); Jaundice (since 24 Nov 2020), Angioplasty (verbatim: history of angioplasty; since 23 Dec 2021), and Splenomegaly (since 31 Jan 2023). The patient was randomly assigned to receive pegcetacoplan 1080 mg twice weekly and received the first dose of IMP in the double-blind treatment period (Part A) on 28 Feb 2023 (Study Day 1).

On 28 Mar 2023 (Study Day 29), the patient's Hb level was low at 63 g/L (reference range: 130 to 170 g/L). On 06 Apr 2023 (Study Day 38), the patient complained of severe shortness of breath and was unable to talk in full sentences, and experienced severe lactic acidosis and compensatory respiratory alkalosis secondary to hemolysis. The patient reported consuming excess alcohol. On the same day (06 Apr 2023), the patient was diagnosed with an SAE of Haemolytic anaemia (verbatim: severe anaemia [worsening of haemolytic anaemia]) of severe intensity. The event met the seriousness criteria of hospitalization and an important medical event. The patient was subsequently admitted to the local hospital for further evaluation and received 4 units of blood transfusions overnight. The patient had low Hb of 59 g/dL (reference range: 130 to 170 g/dL) and bilirubin was 37 µmol/L (reference range was not provided). A CT pulmonary angiography showed lung fibrotic changes, cardiomegaly, and pleural effusion, indicating type I respiratory failure. On the same day (06 Apr 2023), the non-SAEs of Cardiac failure (verbatim: heart failure), Pneumonia (verbatim: bronchopneumonia), Scrotal Oedema (verbatim: scrotal oedema), Pleural effusion (verbatim: pleural effusions), Respiratory failure (verbatim: type 1 respiratory failure), and Hypotension (verbatim: hypotension), all of moderate severity were reported. On 07 Apr 2023 (Study Day 39), a non-SAE of Atrial fibrillation (verbatim: atrial fibrillation) of moderate severity was reported. From 07 Apr 2023 (Study Day 39) to 19 Apr 2023 (Study Day 51), the patient's Hb was persistently low, ranging from 49 g/dL to 71 g/dL (reference range: 130 to 170 g/dL). On 12 Apr 2023 (Study Day 44), the patient received plasma exchange for CAD. On 13 Apr 2023 (Study Day 45), the LDH level was 544 IU/L (reference range was not provided). The IMP was withdrawn due to the SAE of Haemolytic anaemia and multiple non-SAEs (with onset 06 Apr 2023 and 07 Apr 2023), with the last dose received during Part A on 03 Apr 2023 (Study Day 35). During hospitalization, the patient received treatment with PRBC transfusions (10 Apr 2023 [1 unit], 14 Apr 2023 [2 units], and 22 Apr 2023 [2 units]), IV magnesium sulfate 2.5 to 5 g as needed, oral potassium 12 to 24 mmol as needed, IV paracetamol 1000 mg as needed,

IV potassium chloride 40 mmol as needed (all from 06 Apr 2023 to 28 Apr 2023); IV metaraminol 1 to 10 mg/hr as needed (on 07 Apr 2023), oral bisoprolol 2.5 mg QD and oral lansoprazole 30 mg QD (from 07 Apr 2023 onwards); IV phytomenadione 10 mg QD and IV ascorbic acid/vitamin B complex TID (frequency was not reported; both from 07 Apr 2023 to 09 Apr 2023); IV amiodarone 900 mg continuous and IV norepinephrine 0.0006 to 0.064 mg/min as needed (both from 07 Apr 2023 to 10 Apr 2023); IV piperacillin sodium/tazobactam sodium 4.5 mg TID (07 Apr 2023 to 14 Apr 2023), topical chlorhexidine 1 application as needed (07 Apr 2023 to 18 Apr 2023); IV calcium chloride/potassium chloride/sodium chloride/sodium lactate 75 to 250 mL/hr as needed, IV sodium glycerophosphate 30 mmol as needed, oral zopiclone 3.75 mg as needed, topical benzalkonium chloride/chlorhexidine hydrochloride/isopropyl myristate/liquid paraffin 1 application as needed, oral chlordiazepoxide 10 to 20 mg as needed (all from 07 Apr 2023 to 28 Apr 2023), SC enoxaparin 40 mg QD (all from 07 Apr 2023 to 26 May 2023); IV butylscopolamine bromide 10 mg once (08 Apr 2023); oral morphine 10 mg as needed (08 Apr 2023 to 25 Apr 2023), oral melatonin 2 mg as needed (08 Apr 2023 to 28 Apr 2023), inhalation salbutamol 2.5/2.5 mg/mL as needed (09 Apr 2023 to 28 Apr 2023); oral paracetamol 1g as needed and oral vitamins NOS 1 tablet QD (both from 11 Apr 2023 onwards); oral nutrients NOS 1 bottle as needed (11 Apr 2023 to 19 Apr 2023); oral thiamine 100 mg QD, oral vitamin B complex 1 tablet QD, and IV furosemide 20 to 80 mg as needed (all from 11 Apr 2023 to 28 Apr 2023); IV calcium gluconate 2.25 mmol as needed (13 Apr 2023 to 28 Apr 2023); oral chlorphenamine 4 mg as needed, oral montelukast 10 mg as needed, oral dexamethasone 20 mg every week, SC daratumumab 1800 mg every week, oral acyclovir 200 mg TID (all from 15 Apr 2023 onwards); oral allopurinol 300 mg QD (15 Apr 2023 to 29 Apr 2023), oral dexamethasone 4 mg two times per week (from 16 Apr 2023 onwards), oral sulfamethoxazole/trimethoprim 960 mg three times per week (from 17 Apr 2023 onwards), oral furosemide 40 mg QD (17 Apr 2023 to 25 Apr 2023), oromucosal artificial saliva 1 spray as needed (17 Apr 2023 to 28 Apr 2023), IV piperacillin sodium/tazobactam sodium 4.5 mg TID (19 Apr 2023 to 23 Apr 2023), IV sodium chloride 250 to 1000 mL as needed (21 Apr 2023 to 28 Apr 2023), oral amoxicillin sodium/clavulanate potassium 500/125 mg/mg TID (23 Apr 2023 to 24 Apr 2023); oral furosemide 60 mg QD and nasal sodium chloride/water 1 application as needed (both from 25 Apr 2023 onwards); nasal fluticasone 27.5 µg as needed (from 26 Apr 2023 onwards), and nasal sodium chloride 1 application as needed (27 Apr 2023 to 28 Apr 2023). On 18 Apr 2023 (Study Day 50), the patient's Hb was 67 g/L (reference range: 130 to 170 g/L). The non-SAE of Pneumonia was resolved by 24 Apr 2023 (Study Day 56). The SAE of Haemolytic anaemia and non-SAEs of Scrotal Oedema, Pleural effusion, Respiratory failure, and Hypotension were resolved by 28 Apr 2023 (Study Day 60). On the same day (28 Apr 2023), the patient was discharged from the hospital. The investigator considered the SAE of Haemolytic anaemia as not related to the IMP and device. The sponsor assessed the SAE of Haemolytic anaemia to be not related to the IMP but considered to be related to the underlying cold autoimmune hemolytic anemia.

On 08 May 2023 (Study Day 70, 35 days after the last dose of the IMP), the patient visited the research site to receive planned PRBC transfusions (3 units) for primary CAD. At arrival, the patient was in a good condition without any complaints. By the end of the transfusion, the patient had fever, felt unwell with rigors and shaking. The patient also experienced dark urine, shortness of breath, requiring 2 liters of oxygen. On the same day, the patient was hospitalized for further evaluation and management. On this day (08 May 2023), the patient was diagnosed with an SAE of Pneumonia (verbatim: hospital acquired pneumonia) of severe intensity. The event met the seriousness criteria of hospitalization and an important medical event. During hospitalization, the

patient experienced paroxysmal atrial fibrillation with rapid ventricular rate, which was reported to be secondary to the patient's infection, fever, and anemia. On an unknown date, a chest x-ray showed an enlarged heart size, bilateral small pleural effusions, and patchy consolidation in the left mid and lower zone and right lower zone. On an unknown date, a chest CT showed overall appearances suggestive of pulmonary edema with likely superadded infection, moderate to large volume bilateral pleural effusion (predominant on the right side), interval increase in the size of the pericardial effusion, and bilateral pleural effusions. This finding was reported as a non-SAE of Pleural effusion (verbatim: bilateral pleural effusion) of moderate severity on 11 May 2023 (Study Day 73). The respiratory team performed chest tapping under ultrasound guidance. The fluid was assessed to be a transudate due to its low protein levels. On an unknown date, the pleural fluid culture results showed no organisms. On 13 May 2023 (Study Day 75), an echocardiogram showed preserved left ventricular ejection fraction (55%), grade 2 diastolic dysfunction, bi-atrial dilatation, moderate tricuspid regurgitation with an increased pulmonary artery systolic pressure of 53 mmHg, and mild to moderate pericardial effusion. On 15 May 2023 (Study Day 77), the pulmonologist consultation reported that the patient's breathlessness was a mixture of acute and chronic pathologies (fluid overload, hospital acquired pneumonia, underlying emphysema with possible chronic obstructive pulmonary disease [history of smoking 30 packs per year], and mediastinal lung nodes). Cardiologists reported that the patient's fluid overload was multifactorial secondary to Pneumonia, recent atrial fibrillation with rapid ventricular rate, severe anemia (secondary to CAD), IV fluid treatment, and hypoalbuminemia. On 24 May 2023 (Study Day 86), the patient's Hb was 75, platelet count was 80, and neutrophil count was 4.09 (units and reference ranges were not provided). Treatment included IV piperacillin sodium/tazobactam sodium 4.5 mg TID (08 May 2023 to 13 May 2023), IV amikacin 1030 mg as needed (09 May 2023 to 11 May 2023), IV furosemide 40 mg as needed (12 May 2023 to 26 May 2023); IV meropenem 500 mg QID and oral clarithromycin 500 mg BID (both from 13 May 2023 to 19 May 2023); oral osmotically acting laxatives 2 sachets as needed (13 May 2023 to 26 May 2023), oral sodium phosphate monobasic 2 tablets as needed (19 May 2023 to 22 May 2023), and oral amoxicillin/clavulanate potassium 500/125 mg TID (23 May 2023 to 28 May 2023). The investigator considered the SAE of Pneumonia as not related to the IMP and device. The SAE of Pneumonia was resolved by 26 May 2023 (Study Day 88), and the patient was discharged from the hospital on the same day (26 May 2023). The action taken with the IMP due to the SAE of Pneumonia was reported as not applicable. The investigator considered the SAE of Pneumonia as not related to the IMP and device. The sponsor assessed the SAE of Pneumonia to be not related to the IMP. The underlying disease (CAD) with cryoglobulinemia, atrial fibrillation, emphysema with possible chronic obstructive pulmonary disease were considered as the risk factors.

Concomitant medications taken within 30 days of the SAEs of Haemolytic anaemia and Pneumonia included oral folic acid 5 mg QD (start date was reported as unknown), SC hydroxocobalamin 1 mg every 3 months (since 2019); oral clopidogrel 75 mg QD and oral nifedipine 20 mg QD (both since Nov 2019), and SC filgrastim 300 µg every week (Oct 2022 to 26 May 2023).

During the study, the patient experienced other non-SAEs of Oedema peripheral, Skin ulcer (skin ulceration [heel of foot]), Cyanosis, Alcohol withdrawal syndrome, Insomnia, Abdominal rigidity, Dry mouth, and Nasal congestion.

The patient did not complete the study as per the protocol due to the SAE of Haemolytic anaemia and Pneumonia, with the last visit reported on 13 Jun 2023 (Study Day 106). The non-SAE of

Cardiac failure was reported as not resolved, while the non-SAEs of Atrial fibrillation and Pleural effusion were reported as resolving at the time of study discontinuation.

Narrative for Patient 490101

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Events (SAEs)
Study medication:	Parts A and B - Pegcetacoplan
Date of first dose:	18 Aug 2023 (Study Day 1)
Date of last dose:	09 Jul 2024 (Study Day 327)
Event preferred term (verbatim term):	1) Syncope (syncope) 2) Breakthrough haemolysis (breakthrough haemolysis) 3) Atrial fibrillation (worsening of atrial fibrillation)
Start/stop dates:	1) 01 Oct 2023 (Study Day 45) / 09 Oct 2023 (Study Day 53) 2) 21 Jul 2024 (Study Day 339) / 27 Aug 2024 (Study Day 376) 3) 08 Aug 2024 (Study Day 357) / 14 Aug 2024 (Study Day 363)
Action taken with the IMP:	Events 1 to 3: Not applicable
Intensity:	1) Severe 2) Moderate 3) Moderate
Relationship per investigator:	Events 1 to 3: Not related
Relationship per sponsor:	Events 1 to 3: Not related
Outcome:	Events 1 to 3: Recovered/Resolved
Led to study withdrawal:	Events 1 to 3: No

Patient 490101 was a 70-year-old White, not Hispanic or Latino female, who was diagnosed with CAD on an unknown date in Jan 2023. Relevant medical history included Hepatitis B (no start or end dates were provided) and Renal adenoma (renal adenom right; 2010 to Feb 2011). Ongoing conditions included Autoimmune thyroiditis (since Apr 2008), Splenic cyst (since 2015), Cardiac failure (cardiac insufficiency right; since 2016); Arteriovenous malformation (arteriovenous malformation coronarsinus right artrium) and Pulmonary hypertension (both since Oct 2016); Atrial fibrillation (paroxysmal atrial fibrillation; since 14 Oct 2016); Palpitations and Supraventricular extrasystoles (both since Mar 2017); Spinal osteoarthritis (degenerative change in cervical vertebrae) and Vertebral foraminal stenosis (stenosis of neuroforamens cervical vertebrae) (both since 2021); Depression (since 2023), Helicobacter gastritis (Gastritis typ B, H. pylori positive; since 23 Jan 2023); Arteriosclerosis coronary artery, Atrial fibrillation (tachyarrhythmia absoluta), Hepatic cyst, and Aortic arteriosclerosis (all since 29 Mar 2023); Diverticulum intestinal (duodenal diverticulum; since 15 May 2023); Mitral valve incompetence and Tricuspid valve incompetence (both since 13 Jun 2023). The patient was randomly assigned to receive pegcetacoplan 1080 mg twice weekly and received the first dose of IMP in the double-blind treatment period (Part A) on 18 Aug 2023 (Study Day 1).

On 15 Sep 2023 (Study Day 29), the patient's vital measurements were abnormal but not clinically significant, with blood pressure measuring 106/57 mmHg (reference range: 90 to 120 / 60 to 80 mmHg), heart rate at 51 bpm (reference range: 60 to 100 bpm), respiratory rate at 15 breaths per minute (reference range: 12 to 18 breaths per minute), and body temperature at 36.5°C (reference range: 36.5 to 37.3°C). On 01 Oct 2023 (Study Day 45), the patient had blackout, fell, and sustained left frontal blunt trauma to the head and suspected vestibular concussion on the left after hitting the head against a glass wall. The patient was unwell for the past 2 to 3 days. On this day (01 Oct 2023), the non-SAEs of Skin laceration (verbatim: scalp laceration) of mild severity and Vertigo (verbatim: vertigo unknown origin) of moderate severity were reported. On the same day (01 Oct 2023), the patient was hospitalized with the diagnosis of an SAE of Syncope (verbatim: syncope) of severe intensity. The SAE of Syncope met the seriousness criteria of hospitalization and an important medical event. It was reported that the patient had a feeling of vertigo on the right side with associated gait and standing ataxia at the time of the fall. Additionally, the patient had multiple episodes of paroxysmal atrial fibrillation in the past. At admission, the patient's ECG and echocardiogram were normal. The active stand test found no evidence of relevant orthostatic dysregulation. A CT scan of the skull and cervical spine showed mild degenerative changes with possible neuroforaminal narrowing at C5/6, without any intracerebral bleeding, bony injuries, or acute ischemia. The SAE of Syncope was confirmed to be due to a pre-automatic pause with bradycardic sinus rhythm caused by beta-blocker therapy (bisoprolol). On 02 Oct 2023 (Study Day 46), an echocardiogram showed left ventricular diastolic dysfunction, bilateral atrial dilatation, mild atrioventricular valve insufficiency, evidence of pulmonary hypertension, enlarged left ventricle with a normal sinus rhythm, and left ventricular ejection fraction of approximately 58%. The patient had a low Hb of 11.4 g/dL (reference range: 12 to 15.6 g/dL). On 04 Oct 2023 (Study Day 48), a follow-up ECG showed bradycardic sinus rhythm with a mean heart rate of 54 bpm that decreased to 44 bpm at night. On 05 Oct 2023 (Study Day 49), a CT of thorax showed slight bilateral lower posterior pleural effusion, which was reported as a non-SAE of Pleural effusion (verbatim: pleural effusions) of mild severity on the same day (05 Oct 2023). A follow-up CT of the skull and cervical vertebra showed findings consistent with the previous scan results (from 01 Oct 2023). Treatment included oral flecainide 100 mg BID (01 Oct 2023 to 01 Dec 2023). The SAE of Syncope and non-SAE of Skin laceration were resolved by 09 Oct 2023 (Study Day 53), and the patient was discharged from the hospital on the same day (09 Oct 2023). On 10 Nov 2023 (Study Day 85), the vital signs were abnormal but not clinically significant. The follow-up vital measurements on the same day were normal. The non-SAE of Vertigo was resolved by 15 Nov 2023 (Study Day 90). The action taken with the IMP due to the SAE of Syncope was reported as not applicable. The investigator considered the SAE of Syncope as not related to the IMP and device. The sponsor assessed the SAE of Syncope to be not related to the IMP, but most likely related to the pre-automatic pause (bradycardic sinus rhythm in a setting of beta-blocker therapy), atrial fibrillation.

On 02 Feb 2024 (Study Day 169), the patient completed Part A and received the first dose of IMP in the open-label treatment period (Part B). The IMP was withdrawn due to the sponsor decision, with the last dose received during Part B on 09 Jul 2024 (Study Day 327).

On 21 Jul 2024 (Study Day 339; 12 days after the last dose of the IMP), the patient was presented to the emergency department with the symptoms of black urine, jaundice, dysphagia, exhaustion, slight nausea, and deterioration of the general condition. On the same day (21 Jul 2024), the patient was diagnosed with an SAE of Breakthrough haemolysis (verbatim: breakthrough haemolysis) of moderate intensity. The event met the seriousness criteria of hospitalization. On 22 Jul 2024 (Study

Day 340), the patient started treatment with IV sutimlimab 6600 mg every 2 weeks and received 2 units of PRBC transfusions on this day (22 Jul 2024). Due to worsening of the hemolysis, manifested as Hb level of 5.0 g/dL, LDH at 1674 U/L, and bilirubin at 6.3 mg/dL (units and reference ranges not provided), the patient was hospitalized on 24 Jul 2024 (Study Day 342). A re-test value for Hb was low at 7.2 g/dL (reference range: 12.5 to 16.0 g/dL). Treatment included IV prednisolone 50 mg once (on 24 Jul 2024) and switched to oral prednisolone 50 mg QD (25 Jul 2024 to 27 Jul 2024) and IV solutions affecting the electrolyte balance 2 liters QD (24 Jul 2024 to 06 Aug 2024), and 2 units of PRBC transfusions (24 Jul 2024 and 25 Jul 2024). On 25 Jul 2024 (Study Day 343), urinalysis revealed the presence of high levels of erythrocytes and leukocytes, measuring 10.6 cells/µL (reference range: -5 cells/µL) and 39.6 cells/µL (reference range: -9 cells/µL). Dose tapering was attempted with oral prednisolone, by reducing it to 15 mg QD (27 Jul 2024 to 29 Jul 2024) and further decreased to 10 mg QD (30 Jul 2024 to 31 Jul 2024). On 30 Jul 2024 (Study Day 348), the patient had low levels of aPTT at <21 seconds (reference range: 24.4 to 34.4 seconds) and blood creatine phosphokinase at 21 U/L (reference range: 34 to 145 U/L). On 31 Jul 2024 (Study Day 349), the haptoglobin was low at <0.10 g/L (reference range: 0.3 to 2.0 g/L). On 01 Aug 2024 (Study Day 350), the patient had low levels of erythrocyte count of 3.06 cells/pL (reference range: 3.9 to 5.1 cells/pL), Hb of 9.7 g/dL (reference range: 12.0 to 15.2 g/dL), hematocrit of 0.301 L/L (reference range: 0.37 to 0.46 L/L), mean platelet volume of 9.1 fL (reference range: 9.4 to 12.2 fL), and decreased functioning of liver at 82.9% (reference range: 89.4 to 99.5%). The patient had high levels of mean cell volume of 98.4 fL (reference range: 85 to 98 fL), platelet count of 383/nL (reference range: 180 to 380/nL), red cell distribution width (RDW SD) of 72.5 fL (reference range: 37 to 46 fL), RDW CV of 20.6% (reference range: 11.6 to 14.7%), reticulocyte percentage of 13.47% (reference range: 0.4 to 1.6%), reticulocyte count of 412.20/nL (reference range: 22 to 76/nL), total bilirubin of 1.7 mg/dL (reference range: 0.3 to 1.2 mg/dL), direct bilirubin of 0.4 mg/dL (reference range: <0.2 mg/dL), and LDH of 561 U/L (reference range: 120 to 247 U/L). Due to further deterioration of the condition, the dose of oral prednisolone was increased to 15 mg QD (01 Aug 2024 to 16 Aug 2024). The patient was stabilized and was discharged from the hospital on 06 Aug 2024 (Study Day 355).

On an unknown date, the patient presented to the emergency department with the symptoms of palpitations and dizziness. Despite repeated administration of bisoprolol (Beloc), the patient's heart rate dropped to only 120 bpm. On 08 Aug 2024 (Study Day 357; 30 days after the last dose of the IMP), the patient was hospitalized with the diagnosis of an SAE of Atrial fibrillation (verbatim: worsening of atrial fibrillation) of moderate severity. The event met the seriousness criteria of hospitalization. An ECG showed absolute arrhythmia with a heart rate of 127 bpm and a left ventricular pattern. The relevant abnormal laboratory parameters included low oxyhemoglobin at 87.4% (reference range: >96%), low creatine kinase at 25 U/L (reference range: 26-192 U/L), high CRP at 1.5 mg/dL (reference range: <0.5 mg/dL), low calcium at 2.18 mmol/L (reference range: 2.20 to 2.55 mmol/L), and low partial thromboplastin time at 21 seconds (reference range: 22 to 29 seconds). The patient continued to be tachycardic with heart rate frequencies reported >130 bpm. The patient received oral apixaban 5 mg BID (from 08 Aug 2024) as thrombosis prophylaxis. On 10 Aug 2024 (Study Day 359), the patient spontaneously converted to sinus rhythm. The patient had low levels of oxyhemoglobin at 88.1% (reference range: >96%), calcium level at 1.08 mmol/L (reference range: 1.12 to 1.32 mmol/L) and 2.08 mmol/L (reference range: 2.20 to 2.55 mmol/L), sodium at 131 mmol/L (reference range: 136 to 145 mmol/L); high levels of potassium at 8.37 mmol/L (reference range: 3.3 to 5.1 mmol/L) and the CRP slightly

improved, but remained high at 1.0 mg/dL (reference range: <0.5 mg/dL). A follow-up ECG showed sinus rhythm with a heart rate of 61 bpm and a left ventricular pattern. During hospitalization, the patient's Hb was low, ranging from 7.9 g/dL to 9.5 g/dL (reference ranges: 11.8 g/dL to 15.8 g/dL and 12.0 g/dL to 16.0 g/dL). The SAE of Atrial fibrillation was resolved by 14 Aug 2024 (Study Day 363), and the patient was discharged from the hospital on the same day (14 Aug 2024). The dose of oral prednisolone was decreased back to 10 mg QD (17 Aug 2024 to 27 Aug 2024). On 19 Aug 2024 (Study Day 368; 41 days after the last dose of the IMP), the patient was re-admitted to the hospital with 1-day history of massive macrohematuria without dysuria, red urine (and had pink urine on the day of admission), and chills. Urinalysis revealed macrohematuria. The patient's urine stick Hb and protein test results were positive. The laboratory investigations showed low levels of aPTT at 20.6 seconds (reference range: 24.4 to 32.4 seconds), total Hb at 11.4 g/dL (reference range: 12.5 to 16.0 g/dL), and hematocrit at 0.306 L/L (reference range: 0.37 to 0.46 L/L); high levels of RDW at 65.3 fL (reference range: 37 to 46 fL), LDH at 596 U/L (reference range: 120 to 247 U/L), total bilirubin at 2.2 mg/dL (reference range: 0.3 to 1.2 mg/dL), and direct bilirubin at 0.47 mg/dL (reference range: <0.2 mg/dL). On 20 Aug 2024 (Study Day 369), the patient had low levels of Hb, ranging from 9.9 g/dL to.10.5 g/dL (reference range: 12.02 to 15.2 g/dL) and hematocrit at 0.303 L/L and 0.292 L/L (reference range: 0.37 to 0.46 L/L); high levels of LDH at 401 U/L and 1162 U/L (reference range: 120 to 247 U/L), RDW at 63.4 fL and 61.6 fL (reference range: 37 to 46 fL), total bilirubin at 1.1 mg/dL (reference range: 0.3 to 1.2 mg/dL), direct bilirubin at 0.31 mg/dL and 0.26 mg/dL (reference range: <0.2 mg/dL), and estimated eGFR (CKD-EPI) at 65.9 and 74.9 mL/min/1.73^2 (reference range: 60 mL/min/1.73^2). The SAE of Breakthrough haemolysis was resolved by 27 Aug 2024 (Study Day 376). On this day (27 Aug 2024), the patient's blood pressure was 118/58 mmHg (reference range: 90 to 120 / 60 to 80 mmHg) and heart rate was 68 bpm (reference range: 60 to 100 bpm). The patient received oral prednisolone 12.5 mg QD (from 27 Aug 2024). On an unknown date, the patient was discharged for an outpatient care. The action taken with the IMP due to the SAEs of Breakthrough haemolysis and Atrial fibrillation was reported as not applicable. The investigator considered the SAEs of Breakthrough haemolysis and Atrial fibrillation as not related to the IMP and device. The sponsor assessed the SAEs of Breakthrough haemolysis and Atrial fibrillation as not related to the IMP but considered it to be likely due to the underlying disease of primary CAD with worsening of disease. The sponsor assessed the SAE of Atrial fibrillation as not related to the IMP but considered the CAD and the patient's elderly age as contributing risk factors. Also, the patient's history of arteriosclerosis of the coronary arteries and right cardiac insufficiency, as well as mitral and tricuspid valve insufficiency were risk factors for the event. The patient also had pre-existing Paroxysmal atrial fibrillation since 2016. Regarding the Breakthrough hemolysis event, the sponsor also considered that it was a post-treatment hemolysis event as in the usual sense hemolysis is called "breakthrough" if occurring during its treatment (Dingli 2024) while this event had onset 12 days after the end of study treatment (as compared to a median half-life for pegcetacoplan of 8.6 days as per the current European Union Summary of Product Characteristics), raising the possibility of a return of disease activity upon treatment discontinuation.

Concomitant medications taken within 30 days of the SAEs of Syncope, Breakthrough haemolysis, and Atrial fibrillation included oral vitamin D NOS 1000 U QD (since an unknown date), oral apixaban 2.5 mg BID (13 Jun 2023 to 14 Aug 2024), oral bisoprolol 2.5 mg BID (since 13 Jul 2023), and oral entecavir 0.5 mg QD (since 07 Aug 2023). Concomitant medications received within 30 days of the SAE of Syncope included oral sertraline 50 mg QD (from an unknown date to 02 Feb 2024), and oral levothyroxine 88 µg QD (14 Oct 2016 to 23 Nov 2023).

Concomitant medications received within 30 days of the SAEs of Breakthrough haemolysis and Atrial fibrillation included oral levothyroxine 75 µg QD (24 Nov 2023 to 11 Jul 2024) and 88 µg QD (since 12 Jul 2024)

During the study, the patient experienced other non-SAEs of Cold type haemolytic anaemia (verbatim: worsening of CAD [due to vaccination]), Nasopharyngitis, Respiratory tract infection, Hypoglycaemia, Oral herpes, Myalgia (verbatim: muscle pain upper and lower leg unknown origin), and Respiratory infection (verbatim: upper lung unknown origin).

The patient did not complete the study as per the protocol due to the sponsor decision, with the last visit reported on 27 Aug 2024 (Study Day 376). The non-SAE of pleural effusion was reported as not resolved at the time of study discontinuation.

Narrative for Patient 810302

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Events (SAEs)
Study medication:	Parts A, B, and C - Pegcetacoplan
Date of first dose:	28 Mar 2023 (Study Day 1)
Date of last dose:	11 Jun 2024 (Study Day 442)
Event preferred term (verbatim term):	1) COVID-19 pneumonia (COVID-19 pneumonia) 2) Osteonecrosis of jaw (Osteonecrosis of jaw)
Start/stop dates:	1) 12 Jul 2023 (Study Day 107) / 22 Jul 2023 (Study Day 117) 2) 08 Sep 2023 (Study Day 165) / 04 Oct 2023 (Study Day 191)
Action taken with the IMP:	1) Not applicable 2) Drug interrupted
Intensity:	1) Moderate 2) Mild
Relationship per investigator:	Both events: Not related
Relationship per sponsor:	Both events: Not related
Outcome:	Both events: Recovered/Resolved
Led to study withdrawal:	Both events: No

Patient 810302 was a 70-year-old Asian, not Hispanic or Latino male, who was diagnosed with CAD on 17 Jul 2019. No other medical history was reported for this patient. Ongoing conditions included Cataract, Gout, Asthma, Rhinitis allergic, and Hypertension (start dates were not provided). The patient was randomly assigned to receive pegcetacoplan 1080 mg twice weekly and received the first dose of the IMP in the double-blind treatment period (Part A) on 28 Mar 2023 (Study Day 1).

On 05 Jul 2023 (Study Day 100), the patient had fever and cold. On the same day (05 Jul 2023), a non-SAE) of COVID-19 (verbatim: COVID-19 infection) of moderate severity was reported. On 12 Jul 2023 (Study Day 107), the patient attended a study visit and eventually tested positive for COVID-19. A CT scan showed COVID-19 pneumonia. On the same day (12 Jul 2023), the patient

was hospitalized with the diagnosis of an SAE of COVID-19 pneumonia (verbatim: COVID-19 pneumonia) of moderate severity. The event met the seriousness criteria of hospitalization and important medical event. The relevant abnormal laboratory parameters included high leukocytes measuring 12.8 × 10^9/L (reference range: 3.3 to 8.6 × 10^9/L), low platelet count at 148 × 10^9/L (reference range: 158-348 × 10^9/L), and high CRP level at 17.14 mg/dL (reference range: 0 to 0.14 mg/dL). Treatment included IV remdesivir 200 mg once (on 12 Jul 2023) and 100 mg once daily (QD) (13 Jul 2023 to 21 Jul 2023), oral paracetamol 400 mg as needed (PRN) (on 13 Jul 2023), and IV meropenem 1 g BID (13 Jul 2023 to 17 Jul 2023). On 20 Jul 2023 (Study Day 115), the CRP level improved, but remained slightly elevated at 0.99 mg/dL (reference range: 0 to 0.14 mg/dL). The SAE of COVID-19 pneumonia was resolved by 22 Jul 2023 (Study Day 117). On the same day (22 Jul 2023), the patient was discharged from the hospital. The non-SAE of COVID-19 was resolved by 09 Aug 2023 (Study Day 135). On this day (09 Aug 2023), the patient's leukocyte and platelet counts were normal. The action taken with the IMP due to the SAE of COVID-19 pneumonia was reported as not applicable. The investigator considered the SAE of COVID-19 pneumonia as not related to the IMP and device. The Sponsor assessed the SAE of COVID-19 pneumonia to be not related to the IMP. It was determined that the patient's underlying condition of primary CAD and medical history of Asthma were contributing factors to the occurrence of this SAE. Additionally, the spread of pandemic and the aerosol mode of transmission of coronavirus ruled out a causal relationship between the SAE and the IMP.

On 02 Sep 2023 (Study Day 159), the patient reported having a right-sided external buccal dental fistula and underwent an incisional drainage of the fistula at a local clinic. On the same day (02 Sep 2023), a non-SAE of Osteomyelitis (verbatim: mandibular osteomyelitis) of mild severity was reported. On 06 Sep 2023 (Study Day 163), the patient's leukocyte and platelet counts were normal. On 08 Sep 2023 (Study Day 165), the patient completed Part A and received the first dose of IMP in the open-label treatment period (Part B). On the same day (08 Sep 2023), the patient was diagnosed with an SAE of Osteonecrosis of jaw (verbatim: osteonecrosis of jaw) of mild severity and was taken to the hospital for further evaluation. The patient was recommended for causative tooth extraction and removal of decayed bone under IV sedation. On 03 Oct 2023 (Study Day 190), the patient was hospitalized for the planned procedures and underwent tooth extraction and sequestrectomy. Treatment included oral cefalexin 250 mg TID, topical fusidate sodium one application QD, and topical white soft paraffin one application QD (all three from 02 Sep 2023 to 08 Sep 2023). The IMP was interrupted for 3 days because of this SAE (dose on 03 Oct 2023 was not administered). The SAE of Osteonecrosis of jaw was resolved by 04 Oct 2023 (Study Day 191). On the same day (04 Oct 2023), the patient was discharged from the hospital. The IMP was resumed on 06 Oct 2023 (Study Day 193). The non-SAE of Osteomyelitis was resolved by 27 Dec 2023 (Study Day 275). The investigator considered the SAE of Osteonecrosis of jaw as not related to the IMP and device. The sponsor assessed the SAE of Osteonecrosis of jaw to be likely related to the previous dental fistula, drainage, and Osteomyelitis, but not to the IMP. The concomitant usage of corticosteroids was deemed to be a risk factor.

On 23 Feb 2024 (Study Day 333), the patient completed Part B and received the first dose of IMP in the open-label maintenance period (Part C). The IMP was withdrawn due to the premature termination of the study by the sponsor, with the last dose received during Part C on 11 Jun 2024 (Study Day 442).

Concomitant medications taken within 30 days of the SAEs of COVID-19 pneumonia and Osteonecrosis of jaw included cyanocobalamin and pirenoxine both given as 1 drop in each eye

four times a day (start dates were unknown); oral febuxostat 10 mg once daily (QD) (since 1990); oral azilsartan 20 mg twice daily (BID), oral cilnidipine 10 mg QD, oral L-carbocisteine 500 mg as needed (PRN), and oral trichlormethiazide 1 mg QD (all since 1995); oral esomeprazole magnesium dihydrate 20 mg QD (since 15 Jan 2022), oral sulfamethoxazole/trimethoprim 0.5 (dose not specified) three times per week (since 25 Jan 2022), and oral prednisolone 20 mg QD (22 Dec 2022 to 12 Jun 2024).

During the study, the patient experienced other non-SAEs of Glaucoma, Macular pseudohole, and Eyelid ptosis.

The patient did not complete the study as per the protocol due to the premature termination of the study by the sponsor, with the last visit reported on 31 Jul 2024 (Study Day 492).

Narrative for Patient 810401

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Event (SAE)
Study medication:	Parts A and B - Pegcetacoplan
Date of first dose:	12 Oct 2023 (Study Day 1)
Date of last dose:	08 Jul 2024 (Study Day 271)
Event preferred term (verbatim term):	Haemolysis (hemolysis)
Start/stop dates:	17 Jul 2024 (Study Day 280) / Ongoing
Action taken with the IMP:	Not applicable
Intensity:	Severe
Relationship per investigator:	Related
Relationship per sponsor:	Not related
Outcome:	Not recovered/Not resolved
Led to study withdrawal:	No

Patient 810401 was an 80-year-old Asian, not Hispanic or Latino female, who was diagnosed with CAD on 22 Feb 2019. No relevant medical history was reported. Ongoing conditions included Chronic gastritis (start date was not specified), Hypertension (since 1973); Gastrooesophageal reflux disease, Dyslipidaemia, Lumbar spinal stenosis, Osteoarthritis (verbatim: Osteoarthritis knees), and Insomnia (all since 1993); Intracranial aneurysm (since 2003), Constipation (since 07 Mar 2019), Bone marrow failure (since Jul 2019), Bronchitis chronic (since 13 Jan 2022), and Mitral valve incompetence (since 13 Apr 2023). The patient was randomly assigned to receive pegcetacoplan 1080 mg twice weekly and received the first dose of the IMP in the double-blind treatment period (Part A) on 12 Oct 2023 (Study Day 1).

On 28 Mar 2024 (Study Day 169), the patient completed Part A and received the first dose of the IMP in the open-label treatment period (Part B). The IMP was withdrawn due to the premature termination of the study by the sponsor, with the last dose received during Part B on 08 Jul 2024 (Study Day 271).

On 11 Jul 2024 (Study Day 274), the patient had low levels of Hb at 89 g/L (reference range: 116 to 148 g/L, erythrocyte count at 1.23×10^{12} cells/L (reference range: 3.86 to 4.92×10^{12} cells/L), hematocrit at 14.4% (reference range: 35.1 to 44.4%), and haptoglobin at <0.2 g/L (reference range: 0.4 to 2.4 g/L); elevated levels of bilirubin at 26.9 µmol/L (reference range: 5.1 to 20.5 µmol/L), direct bilirubin at 11.3 µmol/L (reference range: 0 to 5.1 µmol/L), indirect bilirubin at 15.5 µmol/L (reference range: 0 to 20.5 µmol/L). On 17 Jul 2024 (Study Day 280; 9 days after the last dose of the IMP), the patient experienced an SAE of Haemolysis (verbatim: hemolysis) of severe intensity. The event met the seriousness criteria of hospitalization. On 28 Jul 2024 (Study Day 291), the patient visited the emergency department with the complaints of severe fatigue and poor overall appearance (for the past 10 days). Physical examination revealed pallor of the eyelids and conjunctiva. Blood pressure was 113/65 mmHg, pulse rate was 65 bpm, and temperature was 36.2°C. On this day (28 Jul 2024), the relevant abnormal laboratory parameters included low levels of Hb at 54 g/L (reference range: 116 to 148 g/L), erythrocyte count at 0.77×10^{12} cells/L (reference range: 3.86 to 4.92×10^{12} cells/L), hematocrit at 9.3% (reference range: 35.1 to 44.4%); elevated levels of bilirubin at 2.53 mg/dL (reference range: 0.4 to 1.5 mg/dL), direct bilirubin at 0.79 mg/dL (reference range: 0.1 to 0.4 mg/dL), LDH at 283 IU/L (reference range: 124 to 222 IU/L), and indirect bilirubin at 1.74 mg/dL (reference range was not provided). Blood tests revealed rapidly progressing anemia, and the patient was scheduled for a blood transfusion on the following day. On 29 Jul 2024 (Study Day 292), the patient visited the emergency department and received 2 units of PRBC transfusions. On this day (29 Jul 2024), the patient's blood pressure was 107/49 mmHg, pulse rate was 90 bpm, and temperature was 35.5°C. It was reported that the patient's hemolysis was due to the discontinuation of the IMP. From 29 Jul 2024 (Study Day 292) to 07 Aug 2024 (Study Day 301), the patient had low levels of Hb ranging from 49 to 68 g/L (reference range: 116 to 148 g/L), hematocrit of 8.9 to 10.4% (reference range: 35.1 to 44.4%), erythrocyte count of 0.76 to 0.91×10^{12} cells/L (reference range: 3.86 to 4.92×10^{12} cells/L); elevated levels of bilirubin ranging from 1.86 mg/dL to 2.24 (reference range: 0.4 to 1.5 mg/dL), direct bilirubin of 0.53 to 0.64 mg/dL (reference range: 0.1 to 0.4 mg/dL), indirect bilirubin of 1.33 to 1.6 mg/dL (reference range was not provided), and LDH of 223 to 250 IU/L (reference range: 124 to 222 IU/L). On 01 Aug 2024 (Study Day 295), the patient visited the emergency again and received 2 units of PRBC transfusions. The blood pressure was 119/42 mmHg, pulse rate was 62 bpm, and temperature was 35.5°C. On 07 Aug 2024 (Study Day 301), the patient was hospitalized to initiate rituximab therapy to suppress the progression of hemolysis. The patient received 2 units of PRBC transfusions, IV rituximab 528.75 mg every week, IV dexchlorpheniramine maleate 5 mg every week, and oral ibuprofen 200 mg every week (all from 08 Aug 2024 to 29 Aug 2024). On 09 Aug 2024 (Study Day 303), the patient's Hb level was improved, but remained low at 79 g/L (reference range: 116 to 148 g/L); however, erythrocytes and hematocrit were persistently low at 0.57×10^{12} cells/L (reference range: 3.86 to 4.92×10^{12} cells/L) and 6.5% (reference range: 35.1 to 44.4%), respectively. The patient had elevated levels of CRP at 1.47 mg/dL (reference range: 0 to 0.14 mg/dL), bilirubin at 3.39 mg/dL (reference range: 0.4 to 1.5 mg/dL), direct bilirubin at 0.98 mg/dL (reference range: 0.1 to 0.4 mg/dL), indirect bilirubin at 1.74 and 2.41 mg/dL (reference range was not provided), and LDH at 265 IU/L (reference range: 124 to 222 IU/L). On this day (09 Aug 2024), the patient received 2 units of PRBC transfusions. On 10 Aug 2024 (Study Day 304), the patient was discharged from the hospital. On 15 Aug 2024 (Study Day 309), the patient had low levels of Hb at 81 g/L (reference range: 116 to 148 g/L), erythrocyte count at 1.27×10^{12} cells/L (reference range: 3.86 to 4.92×10^{12} cells/L), and hematocrit at 13.9% (reference range: 35.1 to 44.4%). The action taken with the IMP due to the SAE of Haemolysis was reported as not

applicable. The investigator considered the SAE of Haemolysis as related to the IMP but not related to the device. The sponsor assessed the SAE of Haemolysis to be not related to the IMP but likely related to the underlying CAD and discontinuation of the IMP. In the Sponsor evaluation, the SAE of Haemolysis was related to the weaning effects of the IMP after pegcetacoplan discontinuation rather than to pegcetacoplan, given the rapid aggravation of anemia from 3 days after the end of pegcetacoplan administration (Hb at 89 g/L, LDH isoenzyme 1 was 191 U/L [reference range 120 to 246 U/L] to 20 days after the end of pegcetacoplan administration (Hb at 54 g/L; LDH at 283 IU/L [reference range: 124 to 222 IU/L].

Concomitant medications taken within 30 days of the SAE of Haemolysis included oral amlodipine besilate 2.5 mg and 5 mg QD, oral atorvastatin calcium trihydrate 10 mg QD, oral benfotiamine/cyanocobalamin/pyridoxine hydrochloride 1 capsule BID, oral bisoprolol fumarate 2.5 mg QD, topical camphor/capsicum SPP extract/methyl salicylate 1 application QD, oral celecoxib 100 mg BID, oral folic acid 5 mg BID, oral L-carbocisteine 500 mg BID; oral limaprost alfadex 5 µg BID, topical loxoprofen sodium dihydrate 100 mg QD switched to oral loxoprofen sodium dihydrate 60 mg as needed; oral magnesium oxide 660 mg TID, oral olmesartan medoxomil 40 mg QD, oral omeprazole sodium 20 mg QD (start dates were not provided); ophthalmic pirenoxine 1 drop QID in the left eye and ophthalmic pranoprofen 1 drop QID in the right eye (both since 2020); ophthalmic epinastine hydrochloride 2 drops as needed in both eyes and oral fexofenadine hydrochloride 30 mg as needed (both from 04 Jan 2024 onwards), and transdermal heparinoid 1 application as needed (from 25 Apr 2024 onwards).

During the study, the patient experienced non-SAEs of Thermal burn (verbatim: thermal burns on the back of the left foot), Conjunctivitis allergic, Rhinitis allergic, Induration, Haemorrhage subcutaneous, and Asteatosis (verbatim: asteatosis [buttocks]).

The patient did not complete the study as per the protocol due to the premature termination of the study by the sponsor, with the last visit reported on 29 Aug 2024 (Study Day 323). The SAE of Haemolysis was reported as not resolved at the time of study discontinuation.

Narrative for Patient 950103

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Event (SAE)
Study medication:	Part A – Placebo Parts B and C - Pegcetacoplan
Date of first dose:	24 Jan 2023 (Study Day 1)
Date of last dose:	09 Jul 2024 (Study Day 533)
Event preferred term (verbatim term):	COVID-19 (COVID-19 infection)
Start/stop dates:	17 Apr 2023 (Study Day 84) / 27 Apr 2023 (Study Day 94)
Action taken with the IMP:	Drug interrupted
Intensity:	Mild
Relationship per investigator:	Not related
Relationship per sponsor:	Not related

Study number:	Sobi.PEGCET-101
Reason for narrative:	Serious Adverse Event (SAE)
Outcome:	Recovered/Resolved
Led to study withdrawal:	No

Patient 950103 was a 71-year-old White, not Hispanic or Latino female, who was diagnosed with CAD on 04 Apr 2019. No medical history was reported for this patient. Ongoing conditions included Osteoarthritis (verbatim: arthrosis; since 2007) and Hypertension (verbatim: benign arterial hypertension; since 2011). The patient was randomly assigned to receive placebo 1080 mg twice weekly and received the first dose of placebo in the double-blind treatment period (Part A) on 24 Jan 2023 (Study Day 1).

Starting on 17 Apr 2023 (Study Day 84), the patient had been ill, experiencing general weakness, dry cough, fatigue on minimal exertion, and fever (body temperature of 37.6℃), and received oral paracetamol 500 mg as needed (17 Apr 2023 to 24 Apr 2023). On the same day (17 Apr 2023), an SAE of COVID-19 (verbatim: COVID-19 infection) of mild severity was reported. The event met the seriousness criteria of hospitalization. The patient was symptomatically managed at home initially. The condition eventually worsened, manifested with the symptoms of increased general weakness, sweating, chills, cough with sputum, difficulty breathing, shortness of breath, gasping, palpitations, fatigue on minimal exertion, chest discomfort, dry mouth, loss of appetite, pain in the head and joints, dizziness, difficulty in walking due to general weakness, and fever (body temperature of 38℃). On an unspecified date, a rapid antigen test with nasopharyngeal swab sample showed positive result for coronavirus. A chest x-ray was normal. On 24 Apr 2023 (Study Day 91), the patient was hospitalized for further evaluation and treatment. At admission, a confirmatory rapid antigen test showed positive results for coronavirus. Physical examination revealed blood pressure of 100/60 mmHg, SpO2 of 89%, heart rate of 90 bpm, respiratory rate of 27 breaths per minute, and body temperature of 38℃; pale skin and visible mucus membrane, dewy skin, decreased turgor, rhythmic and muffled heart sounds, weakened pulmonary vesicular breathing in the lower lobes, dry tongue with coating, irregular defecation, and evident varicose veins on the lower limbs. The patient received 3 doses of Pfizer anti-COVID vaccine in the past and denied prior history of COVID-19 infection. The patient's contact with a confirmed COVID-infected person could not be established. An ECG showed even sinus rhythm with a heart rate of 68 bpm and non-specific T-wave changes. Chest x-ray showed enhanced vascular image of the lungs, enhanced hilus with fibrotic deformation, slightly elevated right dome of the diaphragm, and cardiac shadow with slightly enlarged left border. Relevant laboratory investigations showed WBC count at 8.96, neutrophil count at 58.9, red blood cell count at 1.83, Hb at 68, and hematocrit at 18.8 and 20 (units and reference ranges were not provided), monocyte count at 3.5%, lymphocyte count at 35.5%, and CRP at 31 mg (reference ranges were not provided). The IMP was interrupted for 18 days (from 14 Apr 2023 to 02 May 2023) because of this SAE. Treatment included metamizole sodium (unspecified date in Apr 2023 to 26 Apr 2023); dexamethasone, diphenhydramine hydrochloride, hydroxyzine, and omeprazole (all from an unspecified date in Apr 2023 to 27 Apr 2023), and warfarin (from an unspecified date in Apr 2023 to 27 Nov 2023). On 26 Apr 2023 (Study Day 93), the patient was diagnosed with a non-SAE of Haemolytic anaemia (verbatim: worsening of hemolytic anemia) of moderate severity. The patient received 2 units of PRBCs on this day. It was reported to be a laboratory-identified virus acquired hemolytic anemia. The SAE of COVID-19 and non-SAE of Haemolytic anaemia were resolved by 27 Apr

2023 (Study Day 94). The patient's symptoms subsided and was discharged from the hospital in a relatively improved condition on the same day (27 Apr 2023). At discharge, the patient's WBC was 10.22, ESR was 20, CRP was 9 (units and reference ranges were not provided), and lymphocyte count was 27.1% (reference range was not provided). The patient received oral cardiac therapy (unspecified drug and dose) QD, oral colecalciferol/fish oil 1000/2000 (unspecified unit) QD, and oral ursodeoxycholic acid (unknown dose) QD (all from 27 Apr 2023 to 27 May 2023) as prophylaxis for cholestasis. The IMP was resumed on 02 May 2023 (Study Day 99). The investigator considered the SAE of COVID-19 as not related to the IMP and device. The sponsor assessed the SAE of COVID-19 to be not related to the IMP but attributed it to the worldwide SARS-CoV-2 pandemic situation. The underlying CAD was assessed as a risk factor.

On 11 Jul 2023 (Study Day 169), the patient completed Part A and received the first dose of pegcetacoplan in the open-label treatment period (Part B). On 26 Dec 2023 (Study Day 337), the patient completed Part B and received the first dose of pegcetacoplan in the open-label maintenance period (Part C). The IMP was withdrawn due to the premature termination of the study by the sponsor, with the last dose received during Part C on 09 Jul 2024 (Study Day 533).

Concomitant medications taken within 30 days of the SAE of COVID-19 included oral amlodipine/perindopril 8/10 mg QD and oral bisoprolol 5 mg QD (both since 2011); oral acetylsalicylic acid 100 mg QD (since 10 May 2022); oral folic acid 20 mg QD and oral vitamin B12 NOS 1000 mcg QD (both since 27 Dec 2022).

During the study, the patient experienced other non-SAEs of Thrombocytosis, Urinary tract infection × 2 events, Diarrhoea (verbatim: unspecific diarrhea), and hypoprothrombinaemia.

The patient did not complete the study as per the protocol due to the premature termination of the study by the sponsor, with the last visit reported on 03 Sep 2024 (Study Day 589).

14.3.4. Clinical Laboratory Results

Table 14.3.4.1	Hematology: Summary and Change from Baseline – Safety Set
Table 14.3.4.2	Chemistry: Summary and Change from Baseline – Safety Set
Table 14.3.4.3	Urinalysis: Summary and Change from Baseline – Safety Set
Table 14.3.4.4	Coagulation: Summary and Change from Baseline – Safety Set
Table 14.3.4.5	Hematology Abnormalities of CTCAE Grade >=3 by Study Week Until 8 Weeks After EOT – Safety Set
Table 14.3.4.6	Biochemistry Abnormalities of CTCAE Grade >=3 by Study Week Until 8 Weeks After EOT – Safety Set
Table 14.3.4.7	Urinalysis Abnormalities of CTCAE Grade >=3 by Study Week Until 8 Weeks After EOT – Safety Set
Table 14.3.7.1	Summary of ADA to Pegcetacoplan Peptide Moiety – Safety Set
Table 14.3.7.2	Summary of ADA to Polyethylene Glycol Moiety – Safety Set
Figure 14.3.1.11	Individual ADA Titers to Pegcetacoplan Peptide During the Study - Semi-Log Scale – Safety Set

14.3.5. Vital Signs, Physical Examination, and ECG

15. REFERENCES

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16. APPENDICES

The following appendices are included as separate files.

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

16.1.2 Sample Case Report Form

16.1.3 List of Independent Ethics Committees or Institutional Review Boards

16.1.4 List of Investigators and Other Important Participants in the Study

16.1.5 Signatures of Principal or Coordinating Investigators or Sponsor's Responsible Medical Officer

16.1.6 Listing of Patients Receiving Test Drug from Specific Batches, When More Than One Batch Was Used

16.1.7 Randomization Scheme and Codes

16.1.8 Audit Certificates

16.1.9 Documentation of Statistical Methods

16.1.10 Documentation of Inter-laboratory Standardization Methods and Quality Assurance Procedures if Used

16.1.11 Publications Based on the Study

16.1.12 Important Publications Referenced in the Report

16.1.13 Immunogenicity Reports

16.1.14 Pharmacokinetic Report

16.1.15 Pharmacodynamic Reports

16.2 Patient Data Listings

16.2.1 Discontinued Patients

16.2.2 Protocol Deviations

16.2.3 Subjects Excluded from the Analysis

16.2.4 Demographics

16.2.5 Compliance and/or Drug Concentration Data

16.2.6 Individual Response Data

16.2.7 Adverse Event Listings

16.2.8 Listing of Individual Laboratory Measurements

16.2.9 Other Safety Data

16.3 Case Report Forms

16.3.1 CRFs for Deaths, Other SAEs, and Withdrawals for AEs

16.3.2 Other CRFs Submitted

16.4 Individual Patient Data Listing