25 January 2024
EMA/62863/2024
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## ASPAVELI

International non-proprietary name: Pegcetacoplan

Procedure No. EMEA/H/C/005553/II/0011

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| AH50 | Alternative pathway haemolytic complement activity assay |
| ANC | Absolute Neutrophil Count |
| ANCOVA | Analysis of covariance |
| ARC | Absolute reticulocyte count |
| ATC | Anatomical Therapeutic Classification |
| BMI | Body Mass Index |
| BMF | Bone Marrow Failure |
| BMTx | Bone marrow transplantation |
| CH50 | Total haemolytic complement activity |
| CI | Confident interval |
| COVID-19 | Coronavirus disease 19 |
| CSR | Clinical study report |
| CRF | Case report form |
| DMC | Data Monitoring Committee |
| dL | decilitre |
| EC | European Commission |
| ECG | Electrocardiogram |
| EMA | European Medicines Agency |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EVH | Extravascular haemolysis |
| FACIT | Functional Assessment of Chronic Illness Therapy |
| FLAER | Fluorescent aerolysin |
| g | gram |
| GCP | Good Clinical Practicce |
| GPI | Glycosylphosphatidylinositol |
| Hb | Haemoglobin |
| HSC | Hematopoietic stem cell |
| IB | Investigator’s Brochure |
| ICE | Intercurrent event |
| ICF | Informed consent form |
| IPIG | International PNH Interest Group |

| | |
|---|---|
| IRC | Institutional review Board |
| ITT | Intent-to-treat |
| IVH | Intravascular haemolysis |
| LASA | Linear Analog Scale Assessment |
| LDH | Lactate dehydrogenase |
| LLN | Lower limit of normal |
| LS | Least-square |
| MA | Marketing authorization |
| MAA | Marketing authorization application |
| MAC | Membrane Attack Complex |
| MAVE | Major adverse vascular event |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed-effects model for repeated measures |
| mg | milligram |
| MO | Major objection |
| OC | Other concern |
| PD | Pharmacodynamic(s) |
| PEG | Polyethylene glycol |
| PI | Product information |
| PK | Pharmacokinetics |
| PL | Package leaflet |
| PNH | Paroxysmal nocturnal haemoglobinuria |
| PP | Per protocol |
| PRBC | Packed red blood cell |
| QoL | Quality of life |
| RBC | Red blood cell |
| RCP | Randomization controlled periode |
| RMP | Risk management plan |
| RSI | Requested for supplementary information |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SC | Subcutaneous |
| SD | Standard deviation |

| | |
|---|---|
| SE | Standard error |
| SmPC | Summary of Product Characteristics |
| SoC | Standard of care |
| SOC | System organ class |
| TE | Thromboembolic event |
| TEAE | Treatment-emergent adverse event |
| ULN | Upper limit of normal |
| vs. | versus |
| WOCBP | Women of childbearing potential |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Swedish Orphan Biovitrum AB (publ) submitted to the European Medicines Agency on 4 April 2023 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include treatment of adult patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) not previously treated with a complement inhibitor for ASPAVELI, based on final results from study APL2-308. This is a Phase III, randomized, open-label, comparator-controlled study that enrolled adult patients with PNH who had not been treated with a complement inhibitor. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

## *Information relating to orphan designation*

ASPAVELI, was designated as an orphan medicinal product EU/3/17/1873 on 22 May 2017. ASPAVELI was designated as an orphan medicinal product in the following indication: Treatment of PNH.

The public assessment report will need to include a link to this review (1st heading, in the paragraph on the orphan designation). The text should be as follows:

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Aspaveli as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Aspaveli

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0210/2021 on the granting of a product-specific waiver.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### *Protocol assistance*

The MAH did not seek Protocol Assistance at the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Selma Arapovic Dzakula

| Timetable | Actual dates |
|---|---|
| Submission date | 4 April 2023 |
| Start of procedure: | 22 April 2023 |
| CHMP Rapporteur Assessment Report | 22 June 2023 |
| PRAC Rapporteur Assessment Report | 22 June 2023 |
| CHMP Co-Rapporteur Assessment | 28 June 2023 |
| Updated PRAC Rapporteur Assessment Report | 29 June 2023 |
| PRAC Outcome | 6 July 2023 |
| CHMP members comments | 10 July 2023 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 13 July 2023 |
| Request for supplementary information (RSI) | 20 July 2023 |
| CHMP Rapporteur Assessment Report | 10 October 2023 |
| PRAC Rapporteur Assessment Report | 12 October 2023 |
| PRAC Outcome | 26 October 2023 |
| CHMP members comments | 27 October 2023 |
| Updated CHMP Rapporteur Assessment Report | 3 November 2023 |
| Request for supplementary information (RSI) | 9 November 2023 |
| CHMP Rapporteur Assessment Report | 8 January 2024 |
| CHMP members comments | 15 January 2024 |
| Updated CHMP Rapporteur Assessment Report | 18 January 2024 |
| Opinion | 25 January 2024 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

Aspaveli is currently indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are anaemic after treatment with a C5 inhibitor for at least 3 months.

The Applicant is seeking an extension of the marketing authorization (MA) for the following indication:

*"Aspaveli is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia."*

### *Disease or condition*

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired, rare, clonal and potentially life-threatening non-malignant hematologic disease characterized by complement-mediated red blood cell (RBC) haemolysis, with or without haemoglobinuria, an increased susceptibility to thrombotic episodes, and/or some degree of bone marrow dysfunction. The onset of PNH is often insidious. Although there have been reports of spontaneous remission, the course of the disease is generally chronically progressive.

### *Epidemiology*

PNH is an acquired, chronic genetic disorder that affects all populations and both sexes. Although it has been reported globally, the exact worldwide incidence and prevalence remain unknown. In Europe or the United Kingdom (UK), the annual incidence of PNH has been reported as 1.3 to 2.98 per 1,000 000 (Korkama 2018; Hill 2016).

As of July 2017, according to the International PNH Registry population, the European population is well represented (3012/4439 patients from more than 30 countries located in Europe) and median age at disease onset for PNH was 35.5 years. Men and women were both well-represented (female 53 %) within the registry (Schrezenmeier 2020).

### *Biologic features*

No universally accepted classification scheme is available, but the International PNH Interest Group (IPIG) classified PNH into 3 categories:

- classical PNH in which patients have clinical manifestations of haemolysis or thrombosis,
- PNH in the context of other primary bone marrow disorders such as aplastic anaemia or myelodysplastic syndromes,
- subclinical PNH in which patients have low proportions of PNH clones but no clinical or laboratory evidence of haemolysis or thrombosis

Patients with haemolytic PNH tend to have near-physiological platelet and neutrophil counts, lactacte dehydrogenase (LDH) levels more than 2 times the upper physiological limit (indicative of intravascular haemolysis [IVH]), a normocellular bone marrow, an increased reticulocyte count, and a relatively large (usually >50 %) population of PNH granulocytes. Patients with aplastic anaemia PNH (acquired

aplastic anaemia with a low-to-moderate proportion of a PNH clone) are severely pancytopenic. They tend to have hypocellular bone marrow, relatively low absolute reticulocyte counts (ARCs), and low percentages of PNH granulocytes. (De Latour 2008; Socié 2016; Hill 2017; Schrezenmeier 2020).

## *Aetiology and pathogenesis*

The natural history of patients with PNH is highly variable. The disease can arise de novo or evolve from acquired aplastic anaemia. In PNH, stem cells acquire a gene mutation resulting in the production of abnormal blood cells.

Defective RBCs, white blood cells, and platelets lack the connector glycosylphosphatidylinositol (GPI) for 2 important surface proteins (CD55 and CD59) that regulate complement activity. Lack of these surface proteins make the RBCs susceptible to destruction by the body's own complement system. The lack of GPI results in the complement protein C3 becoming unregulated, which triggers all downstream effectors that ultimately cause destruction of blood cells (haemolysis) and formation of life-threatening blood clots (thrombosis) (Hillmen 2021).

The pathophysiology of PNH involves uncontrolled complement activation, resulting in intravascular haemolysis and extravascular haemolysis (EVH). It is uncontrolled complement activation that leads to IVH mediated by the C5-dependent membrane attack complex and EVH mediated by accumulation of C3 fragments on red blood cell (RBC) surface.

## *Clinical presentation*

The haemolysis can result in a range of debilitating consequences as well as transfusion dependence, all of which contribute to the heavy disease burden and reduced quality of life. The most prevalent symptoms are fatigue (80%), dyspnoea (64%), and haemoglobinuria (62%). PNH commonly results in clinically significant hematologic consequences from chronic haemolysis resulting in anaemia, including a marked increase in risk of thromboembolism, which may ultimately lead to target organ damage and death (Schrezenmeier 2014; Schrezenmeier 2020).

Morbidity, common symptoms, and adverse events (AEs) of PNH from large real-world PNH populations were studied in a UK-based cohort and in the International PNH Registry (Hillmen 1995; Schrezenmeier 2014; Socié 2016; Hill 2017; Schrezenmeier 2020).

Anaemia in PNH is often multifactorial and can result from a combination of haemolysis and bone marrow failure (BMF). IVH with moderate-to-severe anaemia, an increased ARC, a normal-to-increased mean corpuscular volume (the average volume of RBCs), and a markedly increased level of LDH are common in haemolytic PNH. Disabling fatigue, can be disproportionate to the degree of anaemia. Fatigue is frequently most intense during a haemolytic attack but was commonly reported to be present at all times.

Smooth muscle dystonia is also common. Abdominal pain, back pain, oesophageal spasm, dyspnoea, and erectile dysfunction (38 % of male patients) are common manifestations associated with haemolytic PNH and are often a direct consequence of IVH and the release of free Hb.

Episodes of jaundice and haemoglobinuria were also commonly reported (~50 % of patients). These signs and symptoms can be constant or paroxysmal and are often exacerbated by infections, surgery, exercise, pregnancy, or excessive alcohol intake. Patients with PNH have an increased risk of chronic kidney disease as a result of long-term IVH. Renal tubular damage can occur from microvascular thrombosis, accumulation of iron deposits, or both.

Other commonly reported symptoms included headache (63 %), scleral icterus (~45 %), chest pain (33.5 %), and confusion (~30 %). Mild-to-moderate pulmonary hypertension has also been reported.

## *Diagnosis and prognosis*

Thrombosis is the most common cause of mortality in PNH (accounting for almost 50 % of deaths before complement inhibition therapy was introduced). PNH-associated thrombotic events (TEs) occur in up to 30 % of patients in Western countries but only <15 % of patients in Asian countries. The proportions of patients with a history of major adverse vascular events (MAVEs) or TEs at baseline correlated significantly with a larger clone size. Thrombosis might occur in aplastic anaemia PNH but is less common than in haemolytic PNH (Hillmen 1995; Socié 2016; Hill 2017; Schrezenmeier 2020).

Morbidity and mortality in PNH have improved substantially over the past 30 years because of increased awareness, monitoring of disease, and improved treatment options for patients with PNH. Analyses of smaller and larger cohorts of patients with PNH show that life expectancy following diagnosis was about 10 and 20 years in the 1990s and 2000s, respectively. Mortality is mostly attributed to events of thrombosis; additional causes include haemorrhage and infection (Hillmen 1995; de Latour 2008; Hill 2010; Kelly 2011; Loschi 2016; Hill 2017).

Bone marrow failure (BMF) is an associated disorder and an important comorbidity. It can occur independently of PIG-A mutations in patients with PNH and can contribute to the clonal expansion of PIG-A mutant hematopoietic stem cells (HSCs). BMF in PNH might be caused by autoimmunity to HSCs, a mechanism similar to that observed in idiopathic aplastic anaemia (Hilmen 1995; Hill 2017).

The proportions of patients with BMF showed an inverse correlation with clone size (5). Many patients in the registry have aplastic anaemia as their primary diagnosis. Overall, 774 (48.1 %) of patients in the registry had been diagnosed with 1 or more types of bone marrow disease, including aplastic anaemia or hypoplastic anaemia (n=701; 43.5 %), myelodysplastic syndromes (n=93; 5.8 %), myelofibrosis (n=7; 0.4 %), and/or acute myeloid leukaemia (n=6; 0.4 %) (Schrezenmeier 2014; Hill 2017; Schrezenmeier 2020).

## *Management*

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

Historically, management of PNH was limited to the use of supportive measures, such as blood transfusions and anticoagulation therapy. The risk of TEs in patients with PNH remained high. Anticoagulation therapy could reduce the risk of thrombosis, but complications, such as haemorrhage, are frequent (Hillmen 1995; Hill 2017).

Bone marrow transplantation (BMTx) and complement inhibitor therapies are the only effective therapies for the treatment of PNH. The only potentially curative therapy for PNH is allogeneic BMTx; however, this procedure is associated with substantial morbidity and mortality. Although bone marrow function may be restored in up to half of patients receiving a transplant, considerable challenges and risks (e.g., graft failure and infection) reserve this option for patients with severe BMF, reoccurring life-threatening thromboembolic incidences, or refractory transfusion-dependent haemolytic anaemia (Parker 2005; Brodsky 2009; Young 2009 Devalet 2015; Sahin 2016).

*Complement inhibitors*

C5 inhibition is the current standard to treat PNH. Eculizumab was authorized in the EU for use in adult patients with PNH in 2007, and ravulizumab received market authorization in 2019. Eculizumab and ravulizumab share a common mechanism of action in that they are humanized monoclonal antibodies that specifically bind to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. A key structural difference between eculizumab and ravulizumab is the substitution of 4 amino acids in the complementarity-determining and Fc regions of eculizumab, which causes an enhanced endosomal dissociation of C5 and recycling to the vascular compartment through the neonatal Fc receptor pathway. This gives ravulizumab a terminal half-life that is 4 times that of eculizumab (Kulasekararaj 2019; Soliris PI; Ultomiris PI, Gavriilaki 2022; Gerber 2022).

C5 inhibition effectively reduces IVH as evidenced by the reduction of LDH. Treatment with C5 inhibitors results in improved outcomes of disease in patients with PNH. Eculizumab reduces haemolysis (i.e., IVH as measured by LDH), fatigue, transfusion requirements, and improvements in quality of life. It is also associated with a 92 % reduction in the risk of TE and improved patient survival (Hillmen 2006; Brodsky 2009; Kelly 2011; Loschi 2016; Socié 2016; Kulasekararaj 2019; Lee 2019).

In a phase 3 clinical study of patients with PNH previously treated with eculizumab and randomized to either ravulizumab or eculizumab, LDH normalization was achieved by 64 of 97 patients (66.0 %) treated with ravulizumab and 58 of 98 patients (59.2 %) treated with eculizumab, and similar proportions of patients on ravulizumab and eculizumab achieved Hb stabilization (~76 %). Taken together, a proportion of patients with PNH still have underlying haemolysis, which may lead to clinically significant sequalae (Ultomiris PI; Hill 2017; Risotana 2019).

*Supportive therapy*

Despite treatment with complement inhibitors, supportive therapy may still be needed to manage ongoing symptoms or manifestations of PNH. Management of PNH with supportive measures does not modify the course of haemolytic PNH and includes RBC transfusions to lessen ongoing haemolysis and reduce anaemia. In addition, folate supplementation remains necessary to support increased erythropoiesis in the bone marrow during ongoing haemolysis. Anticoagulant therapy has been used prophylactically and in the management of thrombosis; however, the risk of thromboembolism remains high. For events of breakthrough haemolysis, corticosteroids can be used but have a potential long-term toxicity. Prior to complement inhibition, iron supplements were used for renal impairment (Hall 2003; de Latour 2008; Young 2008; Brodsky 2009; Devalet 2015).

With the advent of new therapies, PNH treatment is currently moving from C5 inhibitors to proximal inhibitors (Fattizzo 2023; Panse 2023).

## 2.1.2. About the product

Pegcetacoplan (Anatomical Therapeutic Chemical [ATC] code: L04AA54) is a C3 inhibitor administered via subcutaneous (SC) infusion. Currently approved for the treatment of adult patients with PNH still anaemic after at least 3 months of C5 inhibition therapy.

Pegcetacoplan binds to complement protein C3 and its activation fragment C3b with high affinity, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH, EVH is facilitated by C3b opsonization, and IVH is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan exerts broad regulation of the complement cascade by acting proximal to both C3b and MAC formation, thereby controlling the mechanisms that lead to

EVH and IVH. These functions of pegcetacoplan underlie the observed sustained reduction in complement-mediated haemolytic activity in patients with PNH.

The drug substance is manufactured as a white to off-white, porous, solid lyophilized material of low bulk density. Pegcetacoplan solution for SC infusion 1080 mg/20 mL is a sterile, aqueous, acetate-buffered sorbitol solution. The drug product is filled in 20-mL, single-use, clear Type I glass vials.

### 2.1.3. General comments on compliance with GCP

According to the Applicant, this study was GCP-compliant and at the time of submission, no GCP inspection had been requested nor taken place and no inspection was planned.

## *2.2. Non-clinical aspects*

### 2.2.1. Introduction

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

Only an assessment of environmental risk has been provided.

### 2.2.2. Ecotoxicity/environmental risk assessment

The Applicant submitted an update to Phase I screening environmental risk assessment of pegcetacoplan.

The initial ERA from MAA presented a Phase I screening assessment by comparing predicted environmental concentration ($PEC_{surface\ water}$) of pegcetacoplan (0.0031 µg/L) to the action limit for Phase II studies. The MAH refined Fpen as 0.00159%, based on PNH prevalence from literature data (Griffin and Munir, 2017) of 15.9 per million in Europe. The Applicant's approach was considered acceptable. Since the $PEC_{SURFACE\ WATER}$ of pegcetacoplan was below the action limit (0.01 µg/L) and measured partition coefficient was below 4.5, no phase II environmental fate and effects assessment was required.

In this application, the MAH recalculated $PEC_{surface\ water}$ with new Fpen value for PNH. The EMA's estimate of PNH prevalence for orphan designation is 0.4 in 10000 people in EU, corresponding to Fpen value of 0.004%. Using this value, estimated DOSEai of 0.38 g/inh-d (also used in initial ERA) and default values for $WASTE_{inhab}$ and DILUTION, the updated $PEC_{surface\ water}$ for pegcetacoplan for treatment of PNH is 0.0077 µg/L, which is still below the action limit of 0.01 µg/L.

### 2.2.3. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, with the exception of an assessment of environmental risk, which is considered acceptable.

The MAH has recalculated the $PEC_{SURFACEWATER}$ using a Fpen refined based on EMA's prevalence data for PNH (estimated and assessed for the purpose of the orphan designation).

Since $PEC_{SURFACEWATER}$ of pegcetacoplan remains below the action limit of 0.01 µg/L, it is still believed that Aspaveli is unlikely to represent a risk for the environment following its prescribed usage in patients.

## 2.2.4. Conclusion on the non-clinical aspects

No new non-clinical studies are required.

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of pegcetacoplan.

## *2.3. Clinical aspects*

## 2.3.1. Introduction

## GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

**Table 1: Summary of Studies Supporting the Clinical Pharmacology of Pegcetacoplan in the Treatment of PNH**

| **Protocol/design** | **Single center or multicenter**<br>**Location of centers** | **Status** | **Study objectives/primary endpoint**<br>**Study population** | **No. of subjects**<br>**Doses evaluated**<br>**Duration of treatment** | **Sampling points** |
|---|---|---|---|---|---|
| APL-CP0713-1<br>(Study APL-CP0713-1)<br>Phase 1<br>Double-blind, placebo-controlled, single ascending dose | Single center<br>Australia | Complete with CSR | To assess the safety, tolerability, and PK of single ascending doses of pegcetacoplan in healthy adult subjects<br>Age range: 19-55 years inclusive<br>BMI range: ≥18.5 to ≤32.0 kg/m$^2$<br>Weight range: ≥60.0 to ≤80.0 kg | 31 subjects<br>7 Placebo<br>24 Pegcetacoplan<br>Cohort 1:45 mg single SC dose<br>Cohort 2:90 mg single SC dose<br>Cohort 3: 180 mg single SC dose<br>Cohort 4: 360 mg single SC dose<br>Cohort 5: 720 mg single SC dose<br>Cohort 6: 1440 mg single SC dose | PK samples: before dosing and at 1, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 240, 336, 408, 504, 576, 672, and 1008 hours after dosing.<br>PD samples: before dosing and on Days 2, 3, 4, 5, 6, 7, 8, 11, 15, 18, 22, 25, 29, and 43 after dosing |
| APL2-CP-HV-401<br>(Study APL2-CP-HV-401)<br>Phase 1<br>Double-blind, randomized, placebo-controlled single ascending dose | Single center<br>Australia | Complete with CSR | To assess the safety, tolerability, and PK of single doses of pegcetacoplan in healthy adult subjects<br>Age range: 18-55 years inclusive<br>BMI range: ≥18.5 to ≤32.0 kg/m$^2$<br>Weight range: ≥55.0 to ≤90.0 kg | 20 subjects<br>4 Placebo<br>16 Pegcetacoplan<br>Cohort 1: 200 mg single IV dose<br>Cohort 2: 600 mg single IV dose<br>Cohort 3: 1500 mg single IV dose<br>Cohort 4: 2300 mg single IV dose | PK samples: before dosing and at 15 and 30 minutes and 1, 4, 8, and 12 hours after dosing on Day 1, and on Days 2–8, 15, 22, 29, and 43<br>PD samples: before dosing and at 1, 4, and 12 hours after dosing on Day 1, and on Days 2–8, 15, 29, and 43 |

| Protocol/design | Single center or multicenter<br>Location of centers | Status | Study objectives/primary endpoint<br>Study population | No. of subjects<br>Doses evaluated<br>Duration of treatment | Sampling points |
|---|---|---|---|---|---|
| APL-CP1014<br>(Study CP1014)<br>Phase 1<br>Double-blind, randomized, multiple ascending dose | Single center<br>Australia | Complete with CSR | To assess the safety, tolerability, and PK of multiple ascending doses of pegcetacoplan in healthy adult subjects<br>Age range: 18-55 years inclusive<br>BMI range: ≥18.5 to ≤32.0 kg/m$^2$<br>Weight range: ≥60.0 to ≤80.0 kg | 20 subjects<br>4 Placebo<br>16 Pegcetacoplan<br>Cohort 1:30 mg/d SC for 28 days<br>Cohort2:90 mg/d SC for 28 days<br>Cohort 3:180 mg/d SC for 28 days<br>Cohort 4: 270 mg/d SC for 28 days | PK samples: before dosing on Days 1, 3, 4, 5, 6, 8, 15, 22, 28, 29, 35, 42, 56, 70, and 84<br>PK samples were also collected at 1, 2, 4, 8, 12 and 24 hours after dosing on Days 1 and 28.<br>PD samples: before dosing on Days 1, 8, 15, 22, 29, 35, 42, 56, 70, and 84 |
| APL2-101<br>Phase 1<br>Double-blind, randomized, multiple ascending dose | Single center<br>Australia | Complete with CSR | To assess the safety, tolerability, and PK of subcutaneous (SC) pegcetacoplan in different dose regimens (ie, daily, twice per week, and once per week) in healthy adult subjects.<br>Age range: 18-55 years inclusive<br>BMI range: ≥18.5 to ≤32.0 kg/m$^2$<br>Weight range: ≥50.0 to ≤90.0 kg | 40 subjects<br>4 Placebo<br>36 Pegcetacoplan<br>Cohort 1:360 mg/d SC for 28 days<br>Cohort 2:1300 mg twice weekly SC for 28 days<br>Cohort 3:2600 mg once weekly SC for 28 days<br>Cohort 4: 1080 mg twice weekly SC for 28 days<br>Cohort 5: 1080 mg twice weekly (administered using wearable infusor) SC for 28 days | PK samples: before dosing and at 1, 2, 4, 8, 12, and 24 hours after dosing on Day 1 and on Days 3, 4, 5, 6, 8, 15, 22, 23, 24, 25, 26, 27, 28, 29, 35, 42, 56, 70, and 84. On dosing days, samples were collected before dosing.<br>PD samples: before dosing on Days 1, 8, 15, 22, 25, 29, 35, 42, 56, 70, and 84. On dosing days, samples were collected before dosing. |
| APL2-101<br>Phase 1<br>Double-blind, randomized, multiple ascending dose | Single center<br>Australia | Complete with CSR | To assess the safety, tolerability, and PK of subcutaneous (SC) pegcetacoplan in different dose regimens (ie, daily, twice per week, and once per week) in healthy adult subjects.<br>Age range: 18-55 years inclusive<br>BMI range: ≥18.5 to ≤32.0 kg/m$^2$<br>Weight range: ≥50.0 to ≤90.0 kg | 40 subjects<br>4 Placebo<br>36 Pegcetacoplan<br>Cohort 1:360 mg/d SC for 28 days<br>Cohort 2:1300 mg twice weekly SC for 28 days<br>Cohort 3:2600 mg once weekly SC for 28 days<br>Cohort 4: 1080 mg twice weekly SC for 28 days<br>Cohort 5: 1080 mg twice weekly (administered using wearable infusor) SC for 28 days | PK samples: before dosing and at 1, 2, 4, 8, 12, and 24 hours after dosing on Day 1 and on Days 3, 4, 5, 6, 8, 15, 22, 23, 24, 25, 26, 27, 28, 29, 35, 42, 56, 70, and 84. On dosing days, samples were collected before dosing.<br>PD samples: before dosing on Days 1, 8, 15, 22, 25, 29, 35, 42, 56, 70, and 84. On dosing days, samples were collected before dosing. |

| Protocol/design | Single center or multicenter<br>Location of centers | Status | Study objectives/primary endpoint<br>Study population | No. of subjects<br>Doses evaluated<br>Duration of treatment | Sampling points |
|---|---|---|---|---|---|
| APL2-102<br>Phase 1<br>Double-blind, randomized, placebo-controlled, single ascending dose (Japanese population) | Single center<br>US | Complete with CSR | To assess the safety, tolerability, and PK of a single SC dose of pegcetacoplan in healthy Japanese subjects<br>Age range: 18-55 years inclusive<br>BMI range: ≥18.5 to ≤32.0 kg/m$^2$<br>Weight range: ≥45.0 to ≤90.0 kg | 20 subjects<br>4 Placebo<br>16 Pegcetacoplan<br>Cohort 1:180 mg single SC dose<br>Cohort 2:360 mg single SC dose<br>Cohort 3: 720 mg single SC dose<br>Cohort 4: 1440 mg single SC dose | PK samples: before dosing and at 1, 4, 8, and 12 hours after dosing, and on Days 2, 3, 4, 5, 6, 7, 8, 11, 15, 18, 22, 25, 29, and 43<br>PD samples: before dosing on Day 1 and on Days 2, 3, 4, 5, 6, 7, 8, 11, 15, 18, 22, 25, 29, and 43 |
| APL2-CP-PV-205<br>Phase 1<br>Single-dose, open-label nonrandomized, parallel | Single center<br>New Zealand | Complete with CSR | To assess the PK, safety, and tolerability of a single 270-mg SC dose of pegcetacoplan in subjects with renal impairment<br>Age range: 18-80 years inclusive<br>BMI range: ≥18.5 to ≤36.0 kg/m$^2$ | 16 subjects<br>270 mg, single SC dose | PK samples: before dosing and at 1, 2, 4, 8, and 12 hours after dosing on Day 1, and on Days 2–8, 11, 15, 18, 22, 25, 29, and 43<br>PD samples: before dosing and at 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 240, 336, 408, 504, 576, 672, and 1008 hours after dosing |
| APL-CP0514<br>(Pharoah)<br>Phase 1b<br>Open-label, prospective, nonrandomized, single and multiple ascending dose | Multicenter<br>US | Complete with CSR | To assess the safety, tolerability, and PK of single and multiple SC doses of pegcetacoplan in subjects with paroxysmal nocturnal hemoglobinuria (PNH) who are still anemic during treatment with eculizumab<br>Age: ≥18 years<br>Weight: >55.0 kg | 12 (9 unique)[a]<br>Cohort 4: 270 to 360 mg/d SC for up to 729 days | PK samples: before dosing on study days 1, 2, 3, 4, 8, 15, 22, 29, 43, 57, 71, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, 421, 477, 533, 617, and 729<br>PK samples were also collected at 4 hours after dosing on Study Day 1.<br>PD samples: Before dosing on Study Days 1 and 8, and then on the same study days as the PK samples for the remainder of the study |
| APL2-CP-PNH-204<br>(Paddock)<br>Phase 1b<br>Open-label, multiple ascending dose pilot | Multicenter<br>New Zealand, Hong Kong, Malaysia, Thailand, US | Complete with CSR | To assess the safety, tolerability, preliminary efficacy, and PK of multiple SC doses of pegcetacoplan in subjects with PNH who have not received treatment with eculizumab in the past<br>Age: ≥18 years<br>BMI: ≤38.0 kg/m$^2$<br>Weight: >40 kg | 20 subjects<br>Cohort 1: 180 mg/d SC for 4 weeks<br>Cohort 2: 270 or 360 mg/d SC for up to 1 year | PK samples: before dosing on study days (weeks): 1 (1), 2 (1), 3 (1), 8 (2), 22 (4), 29 (5), 43 (7, 8), 71 (11, 12), 85 (13-16), 113 (17-20), 141 (21-24), 169 (25-28), 197 (29-32), 225 (33-36), 253 (37-40), 281 (41-44), 309 (45-48), 337 (49-52) and at follow-up/exit on weeks/days 365 (53), 379 (55), 393 (57), and 414 (60)<br>PD (complement) samples: before dosing on study days (weeks): -30 (–4), 1 (1), 8 (2), 15 (3), 22 (4), 29 (5), 36 (6), 43 (7, 8), 57 (9, 10), 71 (11, 12), 85 (13-16), 113 (17-20), 141 (21-24), 169 (25-28), 197 (29-32), 225 (33-36), 253 (37-40), 281 (41-44), 309 (45-48), 337 (49-52) and at follow-up/exit on weeks/days 365 (53), 379 (55), 393 (57), and 414 (60) |

| **Protocol/design** | **Single center or multicenter**<br>**Location of centers** | **Status** | **Study objectives/primary endpoint**<br>**Study population** | **No. of subjects**<br>**Doses evaluated**<br>**Duration of treatment** | **Sampling points** |
|---|---|---|---|---|---|
| APL2-202<br>(Palomino)<br>Phase 2a<br>Open-label, multiple-dose | Multicenter<br>Bulgaria, Serbia | Complete with CSR | To assess the safety, tolerability, efficacy, and PK of multiple SC doses of pegcetacoplan in subjects with PNH who have not received treatment with eculizumab in the past<br>Age: ≥18 years | 4 subjects<br>270 to 360 mg/d SC for up to 1 year | PK samples: before dosing on study days (weeks): 1 (1), 2 (1), 3 (1), 8 (2), 22 (4), 29 (5), 43 (7, 8), 71 (11, 12), 85 (13-16), 113 (17-20), 141 (21-24), 169 (25-28), 197 (29-32), 225 (33-36), 253 (37-40), 281 (41-44), 309 (45-48), 337 (49-52), 365 (53), 379 (55), 393 (57), and 414 (60)<br>PD (complement) samples: study days (weeks): -30 (–4), 1 (1), 8 (2), 15 (3), 22 (4), 29 (5), 36 (6), 43 (7, 8), 57 (9, 10), 71 (11, 12), 85 (13-16), 113 (17-20), 141 (21-24), 169 (25-28), 197 (29-32), 225 (33-36), 253 (37-40), 281 (41-44), 309 (45-48), 337 (49-52), 365 (53), 379 (55), 393 (57), and 414 (60) |
| APL2-302<br>(Pegasus)<br>Phase 3<br>Open-label, active comparator-controlled | Multicenter<br>Australia, Belgium, Canada, Spain, France, Germany, Japan, Russia, South Korea, UK, US | Complete with CSR | To establish the efficacy and safety of pegcetacoplan compared to eculizumab in subjects with PNH who continue to have Hb levels <10.5 g/dL despite treatment with eculizumab<br>Age: ≥18 years<br>BMI: <35.0 kg/m$^2$ | 80 subjects<br>41 Pegcetacoplan<br>39 Eculizumab<br>1080 mg twice weekly SC for 48 weeks | PK samples: before dosing on study days (weeks): -28 (–4), -21 (–3), -14 (–2), 1 (1), 14 (2), 28 (4), 42 (6), 56 (8), 84 (12), 112 (16), 119 (17), 126 (18), 140 (20), 154 (22), 168 (24), 196 (28), 224-336 (32-48) and at follow-up on weeks/days 54 (378) and 60 (420)<br>PK samples were also collected at 6 hours after dosing on study days (weeks): –28 (–4), 1 (1), 112 (16) and 336 (48).<br>PD (complement) samples: study days (weeks): -28 (–4), -14 (–2), 1 (1), 14 (2), 28 (4), 42 (6), 56 (8), 84 (12), 112 (16), 119 (17), 126 (18), 140 (20), 154 (22), 168 (24), 196 (28), 224-336 (32-48), and at follow-up on days (weeks) 378 (54) and 420 (60) |

| Protocol/design | Single center or multicenter<br><br>Location of centers | Status | Study objectives/primary endpoint<br><br>Study population | No. of subjects<br><br>Doses evaluated<br><br>Duration of treatment | Sampling points |
|---|---|---|---|---|---|
| APL2-308<br><br>(Prince)<br><br>Phase 3<br><br>Open-label, comparator-controlled | Multicenter<br><br>Hong Kong, Malaysia, Philippines, Singapore, Thailand, Columbia, Mexico, Peru | Complete with CSR | To establish the efficacy and safety of pegcetacoplan compared to standard of care (excluding complement inhibitors) in subjects with PNH<br><br>Age: ≥18 years<br><br>BMI: <35.0 kg/$m^2$ | 53 subjects<br><br>35 Pegcetacoplan<br><br>18 SoC<br><br>1080 mg twice weekly SC for 26 weeks | PK samples: before dosing on Study Days (Weeks): 1 (0), 15 (2), 29 (4), 57 (8), 85 (12), 141 (20), and 183 (26) and at follow-up on Day (Week) 211 (30) from subjects in the pegcetacoplan arm<br><br>Subjects in the SoC arm switching to escape therapy with pegcetacoplan had a PK sample on their first day of pegcetacoplan treatment, and then followed the sampling schedule for the pegcetacoplan arm.<br><br>PD (complement) samples: C3 profile at each visit; CH50 and AH50 samples: before dosing on Study Days (Weeks): 1 (0), 15 (2), 29 (4), 57 (8), 85 (12), 141 (20), and 183 (26) and at follow-up on Day (Week) 211 (30) |

## 2.3.2. Pharmacokinetics

For this variation, the applicant added study APL2-308 (which was a randomized, open label, comparator-controlled study that enrolled adult patients with PNH who had not been treated with a complement inhibitor), and performed new PopPK analysis and PKPD analysis that will be detailed below. The applicant's goal is to support the use of pegcetacoplan as a long-term treatment in both complement inhibitor-naïve and complement inhibitor-experienced adult patients with PNH.

Changes in the SmPC that are relevant to PK are:

In section Absorption:

concentrations of pegcetacoplan through Week 48. In complement inhibitor-naïve patients (Study APL2-308) the geometric mean (%CV) steady-state serum concentration at Week 26 was 744 µg/mL (25.5%) with twice weekly dosing. The bioavailability of a subcutaneous dose of pegcetacoplan is estimated to be ~~77~~76% based on population PK analysis.

Distribution

The mean (%CV) volume of distribution of pegcetacoplan is approximately 3.~~9~~96 L (~~35~~21%) in patients with PNH based on population PK analysis.

In section Elimination:

Following multiple subcutaneous dosing of pegcetacoplan in patients with PNH, the mean (%CV) ~~of~~ clearance is 0.~~015 (28~~012 (21%) L/h and median effective half-life of elimination ($t_{1/2}$) is 8.~~0~~6 days as estimated by the population PK analysis.

In section Special populations:

~~Patients~~ Compared with a reference 70 kg patient, the steady-state average concentration is predicted to be approximately 20% higher in patients with a body weight ~~below~~of 50 kg. Patients weighing 40 kg are predicted to have ~~up to 34~~a 45% higher average ~~exposure at steady state compared to a 70 kg subject, based on population PK analysis~~concentration. Minimal data are available on the safety profile of pegcetacoplan for patients with a body weight below 50 kg.

Bioanalytical methods

Bioanalytical Methods for the Measurement of Serum Pegcetacoplan

The validated bioanalytical methods for the measurement of pegcetacoplan concentrations in human serum involve the extraction of pegcetacoplan and the internal standard (d22-pegcetacoplan) from human serum using protein precipitation. After sample preparation, the analytes are injected into a high-performance liquid chromatograph, in which they are separated on a wide-pore reverse-phase column (2.0 × 50 mm; 2.6, 3.0, or 5.0 µm). The analytes are monitored by a mass spectrophotometer (Sciex API 4000/API5500/Thermo Scientific TSQ Vantage) in positive multiple reaction monitoring mode. The resulting ions are filtered through the first quadrupole mass filter (Q1) according to the mass-to-charge ratio (m/z) before proceeding into Q2, where they are fragmented by collision with neutral gas molecules of nitrogen. The fragmented ions are selected as they pass through the subsequent quadrupole mass filter (Q3) and are analyzed when they collide with an electronmultiplier. The multicharged Q1/Q3 transition is 657.9/144.1 m/z for pegcetacoplan and 661.7/147.2 m/z for the stable isotope-labeled internal standard. Matrix-matched standard curves were generated using peak area ratios of pegcetacoplan to internal standard vs concentration. A 1/x2 weighted linear or quadratic regression was performed to generate the relationship between response and concentration.

- Pre-study analytical method validation av21-190-av20-apl202

Calibration is summarised below:

**Table 2: Pre-study analytical method validation calibrations**

| | Nominal Concentrations | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Batch Number | 10.0 (µg/mL) | 20.0 (µg/mL) | 40.0 (µg/mL) | 80.0 (µg/mL) | 200 (µg/mL) | 500 (µg/mL) | 900 (µg/mL) | 1000 (µg/mL) |
| Mean | 10.2 | 20.0 | 38.7 | 75.1 | 194 | 501 | 936 | 1080 |
| S.D. | 0.410 | 1.16 | 1.90 | 4.65 | 9.24 | 15.9 | 44.6 | 70.3 |
| %CV | 4.0 | 5.8 | 4.9 | 6.2 | 4.8 | 3.2 | 4.8 | 6.5 |
| %Bias | 2.0 | 0.0 | -3.3 | -6.1 | -3.0 | 0.2 | 4.0 | 8.0 |
| n | 16 | 17 | 18 | 18 | 18 | 18 | 18 | 16 |

QCs are summarised below:

**Table 3: Pre-study analytical method validation QCs**

| | Nominal Concentration | | | | |
|---|---|---|---|---|---|
| Batch Number | LLOQ (10.0 µg/mL) | LQC (30.0 µg/mL) | MQC (100 µg/mL) | HQC (800 µg/mL) | ULOQ (1000 µg/mL) |
| n | 6 | 6 | 6 | 6 | 6 |
| | Summary Statistics Section | | | | |
| Inter-run Mean | 10.6 | 27.5 | 91.2 | 798 | 1050 |
| Inter-run S.D. | 1.01 | 1.43 | 4.24 | 40.3 | 49.0 |
| Inter-run %CV | 9.5 | 5.2 | 4.6 | 5.1 | 4.7 |
| Inter-run %Bias | 6.0 | -8.3 | -8.8 | -0.3 | 5.0 |
| n | 18 | 18 | 18 | 18 | 18 |

APL-2 samples stored at -70 °C are stable for up to 33 days prior to extraction and analysis.

- In-study report AD21-1248

This analysis tool place from January 6th to July 14th 2021. 254 sample were received (not counting duplicates), 253 sample were analysed. One sample was not analysed due to insufficient volume.

Human serum samples were analyzed for APL-2 according to Alturas Analytics' test method TM20-636 described in the validation report (AV21-190). Study samples were analyzed within 499 days from collection. Long term stability for APL-2 in human serum has been validated for up to 33 days at -70 °C day.

Reasons for reassay were Sample > ULOQ, Sample injected immediately following a >ULOQ sample, and Sample Overdiluted.
Calibration summary is below.

**Table 4: In-study analytical method calibrations**

| | Nominal Concentrations | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Batch Number | 10.0 (µg/mL) | 20.0 (µg/mL) | 40.0 (µg/mL) | 80.0 (µg/mL) | 200 (µg/mL) | 500 (µg/mL) | 900 (µg/mL) | 1000 (µg/mL) |
| Mean | 10.3 | 19.6 | 38.9 | 76.5 | 190 | 516 | 941 | 1040 |
| S.D. | 0.690 | 0.888 | 2.28 | 3.74 | 9.52 | 24.3 | 52.7 | 66.7 |
| %CV | 6.7 | 4.5 | 5.9 | 4.9 | 5.0 | 4.7 | 5.6 | 6.4 |
| %Bias | 3.0 | -2.0 | -2.8 | -4.4 | -5.0 | 3.2 | 4.6 | 4.0 |
| n | 17 | 17 | 17 | 18 | 18 | 18 | 17 | 17 |

QCs are summarised below:

**Table 5: In-study analytical method QCs**

| | Nominal Concentration | | | | |
|---|---|---|---|---|---|
| Batch Number | LQC (30.0 µg/mL) | MQC (100 µg/mL) | HQC (800 µg/mL) | DQC [a] (800 µg/mL) | DQC [b] (800 µg/mL) |
| Mean | 28.6 | 95.4 | 820 | 823 | 777 |
| S.D. | 2.17 | 8.55 | 58.4 | 34.4 | 45.7 |
| %CV | 7.6 | 9.0 | 7.1 | 4.2 | 5.9 |
| %Bias | -4.7 | -4.6 | 2.5 | 2.9 | -2.9 |
| n | 18 | 18 | 18 | 9 | 12 |

[a] = Dilution QCs undiluted concentration 800 µg/mL; a 2-fold dilution with blank matrix was performed prior to extraction and analysis.
[b] = Dilution QCs undiluted concentration 800 µg/mL; a 5-fold dilution with blank matrix was performed prior to extraction and analysis.

ISR was performed on 27 samples, all passed with less than 20% deviation.

Bioanalytical Methods for Monitoring Immunogenicity

Immunogenicity testing of samples from early clinical studies (Study APL-CP0713-1, Study APL-CP1014, Study APL2-CP-HV-401, Study APL-CP0514, and 6 subjects from Study APL2-CP-PNH-204) was performed using the Intertek antidrug antibody (ADA) assay. The assay results were reported as ADA response to the whole molecule of pegcetacoplan. More-specific ADA assays were later developed, one specific for antibodies against the peptide moiety of pegcetacoplan (anti–pegcetacoplan peptide antibody assay) and a second one specific for antibodies against the PEG component of pegcetacoplan (anti-PEG antibody assay). A competitive ligand-binding neutralizing antibody (NAb) assay has also been developed and validated to detect pegcetacoplan NAbs.

Drug tolerance was subsequently found to be unacceptable for the anti-pegcetacoplan peptide ADA and NAb assays. Redevelopment and revalidation work for both assays are ongoing. More specifically, a sensitive assay is being developed to detect and monitor the presence and titer of antibodies that bind the active moiety of pegcetacoplan. The assay will be capable of detecting antipegcetacoplan antibodies in the presence of pegcetacoplan at serum concentrations that are expected at the time of patient sampling. Furthermore, a sensitive assay that is able to evaluate the neutralizing activity of anti-pegcetacoplan antibodies detected in patient samples is being developed. Based upon successful validation of these sensitive assays to establish the incidence, titer, and neutralizing activity of antibodies to pegcetacoplan, samples from studies APL2-302 and APL2-308 will be reanalysed to establish whether there is an impact on safety and efficacy of pegcetacoplan.

**ADA Assays**

ELISA-Based Antidrug Assay (Intertek ADA Assay): A precise, sensitive, and reproducible method was validated at Intertek for the qualitative determination of antidrug antibodies to pegcetacoplan in human serum using a direct enzyme-linked immunosorbent assay (ELISA). In this assay, samples are incubated for 1 hour with pegcetacoplan that has been immobilized on an ELISA plate. After incubation, the plate(s) are washed with high salt wash buffer and the bound antibodies are detected with goat anti-human IgG/A/M– horseradish peroxidase (HRP) (rabbit anti-mouse IgG-HRP for the mouse anti-PEG-positive control) and then visualized with a 3,3′ ,5,5′ -tetramethylbenzidine substrate solution. The color development is stopped when the most concentrated positive control has an optical density of approximately 0.6 at the 650- nm wavelength. The intensity of the color is subsequently measured at 450 nm with a 650-nm wavelength correction.

Electrochemiluminescence-Based Anti–Pegcetacoplan Peptide Antibody Assay: For both the screening and titer assays (BioAgilytix and Q2 methods), anti-PEG antibodies are removed in a first step as follows: streptavidin-coated magnetic beads are incubated with biotinylated PEG. Samples, positive control, and negative controls are thawed at room temperature and then diluted to the minimum required dilution (MRD; 1:10 dilution) in casein blocking buffer in a 96-well polypropylene plate. The diluted samples are then combined with the beads in the plate and moved to a refrigator set to 4 ☐C for overnight incubation while shaking.

In parallel, the appropriate wells of a Meso Scale Discovery (MSD) standard bind 96-well plate are coated with 50 µL of 2 µg/mL pegcetacoplan coat stock, and control wells are coated with 100 ng/mL human IgG, or 100 ng/mL human IgM in 1× phosphate-buffered saline buffer and incubated at room temperature overnight. On the next day, the polyproylene plate containing the mixed beads and samples is removed from the refrigerator and brought to room temperature. The plate is placed on a plate magnet, and 150 µL of supernatant is transferred to a new polypropylene plate. Then 50 µL of supernatant is transferred in duplicate to the MSD plate. The MSD plate is then sealed and incubated for 60 to 90 minutes at room temperature with shaking. The plate is washed, inverted, and tapped dry on absorbent paper, and 50 µL of detection antibody cocktail (5 ng/mL anti-mouse-rabbit IgG-ruthenium, 1 ng/mL anti-human IgMruthenium, and 2.5 ng/mL anti-human IgG-ruthenium) is added to the appropriate wells of the plate. The plate is sealed, incubated at room temperature, washed, inverted, and tapped dry on absorbent paper, and 150 µL of 2× Read Buffer T is added to the plate. The plate is read on MSD Imager 600 Reader immediately after buffer addition.

The confirmatory assay procedure is the same as described above for the screening and titer assays with the exception that the samples and controls are diluted to the MRD in buffer that contains 4 µg/mL of pegcetacoplan and incubated and shaken for 30 to 60 minutes at room temperature.

Anti-PEG Antibody Assay: For both the screening and titer assays (BioAgilytix and Q2 methods), streptavidin-coated magnetic beads are incubated with biotinylated PEG. Samples, positive control,

and negative controls are thawed at room temperature and then diluted to the MRD (1:10 dilution) in casein blocking buffer in a 96-well polypropylene plate. The diluted samples are then combined with the beads in the plate and moved to a refrigator set to 4°C for overnight incubation while shaking. In parallel, wells of a Maxisorp 96-well plate are coated with multi-PEGylated bovine serum albumin in carbonate coating buffer, human IgG, or human IgM in 1× phosphate-buffered saline and incubated at room temperature overnight. On the next day, the wells of the coated Maxisorp plate are washed and dried, and then casein buffer is added to all wells of the plate. The plate with beads is then placed on top of a magnet to remove the supernatant and wash the beads. The anti-PEG antibodies are then dissociated from the beads with 0.3 M acetic acid, and the plate is placed on a magnet. The acidified supernatant is neutralized by transferring from the bead plate to a fresh polypropylene plate with 1 M Tris-HCl (pH 9.5) in the appropriate wells. The neutralized bead extraction supernatant containing any anti-PEG antibodies is added to the blocked Maxisorp plate. The plate is then sealed, incubated at room temperature, washed, inverted, and dried, and detection antibody cocktail (anti-mouse-HRP and anti-human IgG-HRP) is added to the appropriate wells of the plate. The plate is then washed, inverted, and tapped dry, followed by addition of 3,3′,5,5′-tetramethylbenzidine substrate. The color development is monitored and stopped, and the plate is read on a plate reader for absorbance at 450 nm (detection).

The confirmatory assay procedure is the same as described above for the screening and titer assays with the exception that the samples and controls are diluted to the MRD in buffer that contains 400 µg/mL of 40-kDa PEG and incubated for 45 to 60 minutes at room temperature.

**NAb Assay**

This competitive ligand-binding NAb assay (BioAgilytix method) was developed to detect pegcetacoplan NAbs in the presence of endogenous C3 levels, the target of pegcetacoplan.

Initially, a protein A/G/L Sepharose column is used to bind most immunoglobulins present in a given sample. This step is performed to separate potential NAbs from the high circulating concentration of C3. Samples are then eluted from the Sepharose column with 0.1 M glycine at pH 2.5 and neutralized with 1 M Tris at pH 9.0 on a pegcetacoplan-coated MSD standard bind plate. Any NAb present will bind pegcetacoplan and compete with a sulfo-tagged human C3 protein. The more NAb present, the less sulfo-tagged human C3 will bind and the less electrochemiluminescence signal will be produced.

**Modeling and simulation methods**

Population analysis report APL-EX21-CP-010

A PopPK analysis (Report APL-EX21-CP-010) was completed for pegcetacoplan using the data from 11 clinical studies (N = 284 subjects), including those completed in healthy subjects, subjects with renal impairment, and subjects with PNH. The goals of the analysis were as follows:

• to update the PopPK model to include data from all of Study APL2-302 and from Study APL2-308, including assessment of the impact of intrinsic and extrinsic factors.

Subjects and studies included are detailed below.

**Table 6: Studies, subjects and samples included in the updated population PK analysis**

| Study | Study Population/ Dose Route | No. of Subjects | Quantifiable | Post-dose BLQ | Total |
|---|---|---|---|---|---|
| Study 101 | Healthy/SC | 36 | 848 | 22 | 870 |
| Study CP1014 | | 16 | 364 | 30 | 394 |
| Study 102 | | 16 | 232 | 49 | 281 |
| Study CP0713-1 | | 24 | 390 | 26 | 416 |
| Study 401 | Healthy/IV | 16 | 272 | 0 | 272 |
| Study 205 | Renal Impairment/SC | 16 | 262 | 42 | 304 |
| Study 202 | PNH/SC | 4 | 73 | 1 | 74 |
| Study 204 | | 22 | 387 | 7 | 394 |
| Study CP0514 | | 9 | 203 | 21 | 224 |
| Study APL2-302 | | 80 | 1503 | 260 | 1763 |
| Study APL2-308 | | 45[a] | 203 | 0 | 203 |
| **Total** | | 284 | 4737 | 458 | 5195 |
| **Post-dose BLQ (%)** | | | | 8.8% | |

BLQ = below the limit of quantification; SC = subcutaneous; IV = intravenous; PNH = paroxysmal nocturnal hemoglobinuria

[a] The analysis dataset included 46 subjects for Study APL2-308; however, 1 subject (APL2-308-37149003) had no quantifiable PK samples and was excluded from data summaries.

Subjects from Study APL2-308 were primarily of Asian race (32/45, 71.1%). Subjects were relatively evenly distributed across sex (44.4% female; 55.6% male) and patient status (43.7% healthy subjects; 56.3% PNH patients). All subjects from Study APL2-302 were receiving eculizumab at baseline while all subjects from Study APL2-308 were eculizumab treatment naive. The median age of all subjects was 36 years (range: 19-81 years). Notably, the median body weight for subjects from Study APL2-308 (61.8 kg [range: 41-95 kg]) was lower than the median body weight for subjects from Study APL2-302 (72.4 kg [range: 51-156 kg]) and from all studies (70.0 kg [range: 41-156 kg]). Additionally, median aspartate aminotransferase (AST) levels were higher in Study APL2-308 (85.0 IU/L [range: 20-231 IU/L]) compared to values pooled across all studies (23.0 IU/L [range: 6-302 IU/L]). The median baseline C3 level across all subjects was 1.00 g/L (range: 0.470-1.64 g/L).

Observed pegcetacoplan and C3 concentration-time curves are overlaid on the pooled data from both Study APL2-302 and Study APL2-308 stratified by analyte below. These plots demonstrate higher pegcetacoplan exposure on average in Study APL2-308 compared to Study APL2-302, which does not appear to be explained by differences in C3 level over time.

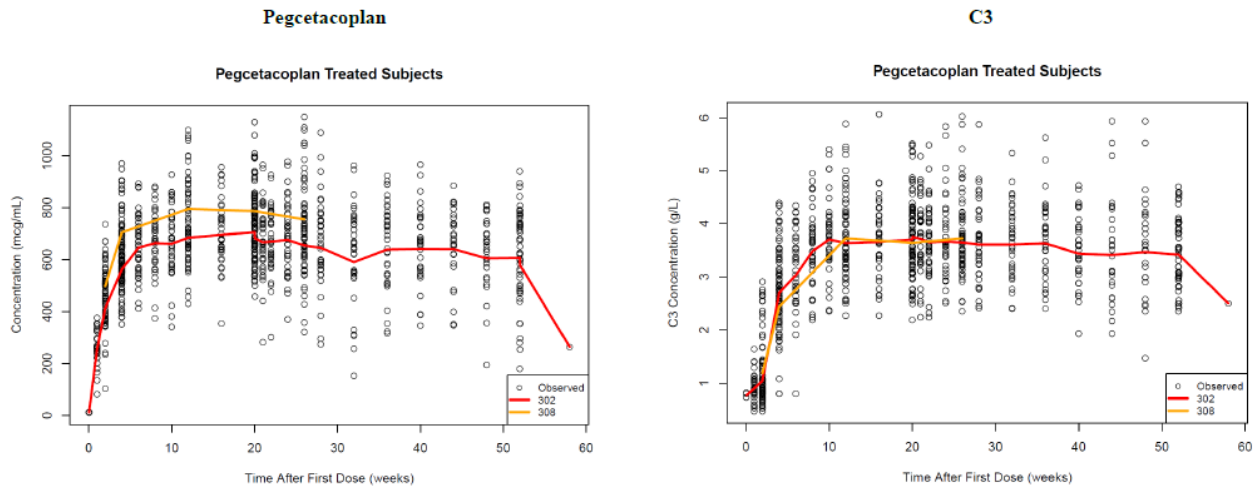



**Figure 1: Comparison of pegcetacoplan and C3 vs time in different studies**

The PK model structure included 1-compartment disposition, transit compartment absorption via the SC route, IV administration directly into the central compartment, and first-order elimination, which adequately described the serum concentration-time profile of pegcetacoplan in healthy adults, adults with renal impairment, and adult patients with PNH.

In Study APL2-302, the observed concentration-time data are generally contained within the simulated 90% CIs in these plots, indicating that the reference model (including only RCP data) adequately predicts the concentration-time profile of pegcetacoplan throughout the entire Study APL2-302 duration. These predictions are adequate for both patients originally randomized to pegcetacoplan and eculizumab-to-pegcetacoplan switch patients.

In Study APL2-308, the separation between the observed 50th percentile (median) and simulated 90% CI suggests that the central tendency of the pegcetacoplan concentration-time profile is slightly underpredicted with the reference model, though variability is adequately captured at the extremes (5th and 95th percentiles).

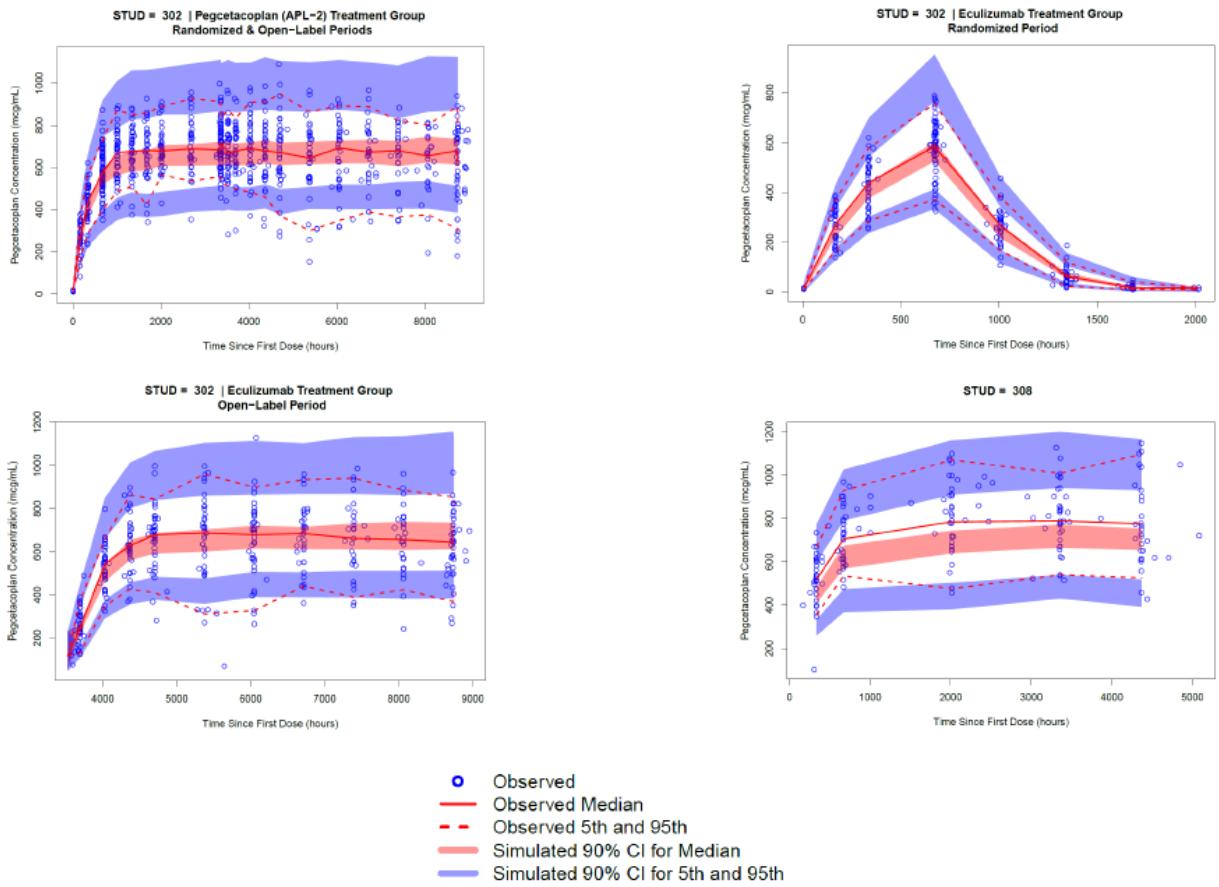



**Figure 2: External VPcs for studies APL2-302 and APL2-308**

*Evaluation of covariates*

Covariates of interest evaluated in the previous analysis were reassessed by including all covariates simultaneously following a full model approach.

**Table 7: Covariates in full model**

| Parameter | Covariates Evaluated |
|---|---|
| KA | Categorical: patient status (reference: healthy subject); sex (reference: male)<br>Continuous: BMI (reference: 25 kg/m$^2$) |
| CL | Categorical: patient status (reference: healthy)[a], sex (reference: male), Asian race (reference: other races), baseline eculizumab treatment status (reference: eculizumab naïve)<br>Continuous: body weight (reference: 70 kg)[a], age (reference: 35 years), creatinine clearance (reference: 120 mL/min), AST (reference: 20 IU/L), ALT (reference: 20 IU/L), total bilirubin (reference: 1.2 mg/dL), albumin (reference: 4.3 g/dL) |
| V2 | Categorical: patient status (reference: healthy)[a], sex (reference: male), Asian race (reference: other races), baseline eculizumab treatment status (reference: eculizumab naïve)<br>Continuous: body weight (reference: 70 kg), age (reference: 35 years), albumin (reference: 4.3 g/dL) |

KA = first-order absorption rate constant; CL = clearance; V2 = volume of the central compartment; BMI = body mass index; AST = aspartate aminotransferase; ALT = alanine aminotransferase

[a] Indicates covariates included in the preliminary updated model. These covariates are treated as structural and not subject to covariate selection

A reduced full covariate model was subsequently developed by removing the following 9 non-structural covariates that were poorly estimated (relative standard error >100%): female sex, age, and CrCL on CL; PNH patient status, baseline eculizumab treatment status, female sex, and age on V2; PNH patient status and female sex on KA. The change in OFV with the removal of these 9 covariate-parameter relationships was 5.881, which is less than the threshold value for retention of a covariate-parameter relationship for a single degree of freedom during the backward elimination procedure (ΔOFV > 10.8, $p < 0.001$).

A stepwise backward elimination procedure based on the likelihood ratio test was used to identify the final updated model containing similar 'information' content as the reduced full covariate updated model, but with fewer covariates. At each step, the covariate-parameter relationship which had the lowest change in OFV and did not meet the inclusion criteria (ΔOFV >10.8 [$p<0.001$]) was eliminated and the stepwise backward elimination procedure was repeated until all covariate-parameter relationships met the inclusion criteria. All 9 of the remaining non-structural covariates in the reduced full covariate model were removed. Therefore, there were no covariates retained in the final updated model that were not included in the preliminary updated model.

Because no additional non-structural covariate effects were retained in covariate selection, the preliminary updated PK model was declared the final updated PK model.

*Final updated PK model*

**Table 8: PK parameter estimates for the final updated popPK model**

| Theta/Parameter (Units) | Estimate | ASE | %RSE | 95% CI |
|---|---|---|---|---|
| 1 TVCL (L/hr) | 0.0117 | 0.000577 | 4.94 | (0.0106-0.0128) |
| 2 TVV2 (L) | 3.96 | 0.196 | 4.96 | (3.57-4.34) |
| 3 TVKA ($hr^{-1}$) | 0.0370 | 0.00138 | 3.73 | (0.0343-0.0397) |
| 4 F1 | 0.758 | 0.0389 | 5.13 | (0.681-0.834) |
| 8 Lyophilized formulation on F1 | 0.220 | 0.0385 | 17.5 | (0.145-0.296) |
| 9 PNH on CL | 0.257 | 0.0302 | 11.8 | (0.197-0.316) |
| 10 WT on CL | 0.646 | 0.0666 | 10.3 | (0.515-0.776) |
| 11 WT on V2 | 0.809 | 0.0847 | 10.5 | (0.643-0.975) |
| **Residual Variability (%)** | | | | |
| 5 RE Healthy Subjects | 20.0 | | | (19.4-20.6) |
| 6 RE PNH Phase 1 and 2 | 32.6 | | | (30.7-34.6) |
| 7 RE PNH Phase 3 | 16.3 | | | (15.7-16.9) |
| **IIV (CV, %)** | | | | |
| ETA1 – CL | 20.9 | | | (18.8-22.9) |
| ρ(ETA1-CL, ETA2-V2) | 0.571 | | | – |
| ETA2 – V2 | 21.4 | | | (18.6-23.8) |
| ETA3 – KA | 52.5 | | | (46.0-58.5) |
| **OFV** | –8708.818 | | | |
| **CN** | **90** | | | |

Abbreviations: %RSE = percentage relative standard error; ASE = asymptotic standard error; CN = condition number; CV = coefficient of variation; ETA= interindividual random effect parameter sampled from N(0, ω2); F1 = subcutaneous bioavailability; hr = hour; IIV = interindividual variability; KA = absorption rate constant; OFV = objective function value; Phase 1 and 2 = Phase 1 and 2 patient studies; Phase 3 = Phase 3 patient studies; PNH = patients with paroxysmal nocturnal hemoglobinuria; RE = proportional residual error; TVCL = typical value of clearance; TVV2 = typical value of volume of the central compartment; TVKA = typical value of first-order absorption rate constant; V2 = volume of distribution of central compartment; WT = body weight.

Notes: CV calculated as $\left(\sqrt{\exp(\omega^2) - 1}\right) \cdot 100\%$. η-shrinkage: 4.8% ($\eta_1^{CL}$), 15.8% ($\eta_2^{V2}$), 17.4% ($\eta_3^{KA}$).

The following equations describe the covariate-parameter relationships in the preliminary updated model:

$$CL_i = TVCL \cdot (1 + PNH \cdot \theta_9) \cdot \left[\frac{WT_i}{70}\right]^{\theta_{10}} \cdot exp\,(\eta_i^{CL})$$

$$V2_i = TVV2 \cdot \left[\frac{WT_i}{70}\right]^{\theta_{11}} \cdot exp\,(\eta_i^{V2})$$

$$KA_i = TVKA \cdot exp\,(\eta_i^{KA})$$

$$F1 = TVF1 \cdot (1 + FORM4 \cdot \theta_8)$$

where parameters are defined as follows:

- $CL_i$ is the clearance for the $i^{th}$ subject; $TVCL$ is the typical value of CL ($\theta_1$); $\eta_i^{CL}$ is a random effect describing the $i^{th}$ individual's deviation from the population CL.
- $\theta_9$ is the proportional change in CL for patients with PNH relative to healthy subjects.
- $\theta_{10}$ is the power describing the relationship between $WT_i$ and CL centered on a body weight of 70 kg, where $WT_i$ is the baseline body weight for the $i^{th}$ subject.
- $V2_i$ is the central volume of distribution for the $i^{th}$ subject; $TVV2$ is the typical value of V2 ($\theta_2$); $\eta_i^{V2}$ is a random effect describing the $i^{th}$ individual's deviation from the population V2.
- $\theta_{11}$ is the power describing the relationship between $WT_i$ and V2 centered on a body weight of 70 kg, where $WT_i$ is the baseline body weight for the $i^{th}$ subject.
- $KA_i$ is the first-order absorption rate constant for the $i^{th}$ subject; $TVKA$ is the typical value of KA ($\theta_3$); $\eta_i^{KA}$ is a random effect describing the $i^{th}$ individual's deviation from the population KA.
- $F1$ is the subcutaneous bioavailability; TVF1 is the typical value of F1 ($\theta_4$).
- $\theta_8$ is the fractional change in F1 with the lyophilized formulation (FORM 4 = 1 if lyophilized formulation and 0 if sorbitol, mannitol, or dextrose formulation).

Source: Report APL-EX21-CP-010 Table S1.

The final updated model included the following covariate-parameter relationships: lyophilized formulation on subcutaneous bioavailability (F1), PNH patients (relative to healthy subjects) on clearance (CL), body weight on CL, and body weight on volume of the central compartment (V2).

To further evaluate and quantify the observed deviation of Study APL2-308 from other PNH studies, a sensitivity analysis was performed by adding a study effect covariate for Study APL2-308 on CL. The final updated model served as the reference model for this sensitivity analysis.

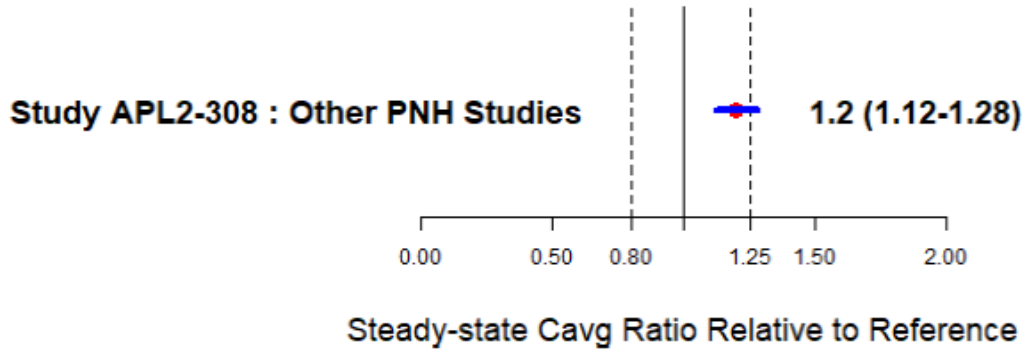
**Table 9: Pharmacokinetic Parameter Estimates for the Sensitivity Analysis Including a Study APL2-308 Effect on CL**

| Theta / Parameter (Units) | Estimate | ASE | %RSE | 95% CI |
|---|---|---|---|---|
| 1 TVCL (L/hr) | 0.0117 | 0.000565 | 4.82 | (0.0106; 0.0128) |
| 2 TVV2 (L) | 3.97 | 0.193 | 4.86 | (3.59; 4.35) |
| 3 TVKA ($hr^{-1}$) | 0.0370 | 0.00138 | 3.72 | (0.0343; 0.0397) |
| 4 F1 | 0.755 | 0.0379 | 5.02 | (0.680; 0.829) |
| 8 Lyophilized Formulation on F1 | 0.226 | 0.0381 | 16.9 | (0.151; 0.301) |
| 9 PNH on CL | 0.305 | 0.0321 | 10.5 | (0.242; 0.368) |
| 10 WT on CL | 0.566 | 0.0668 | 11.8 | (0.435; 0.697) |
| 11 WT on V2 | 0.783 | 0.0836 | 10.7 | (0.619; 0.947) |
| 12 Study APL2-308 on CL | -0.164 | 0.0322 | 19.6 | (-0.228; -0.101) |
| **Residual Variability (%)** | | | | |
| 5 RE Healthy Subjects | 20.0 | | | (19.4; 20.6) |
| 6 RE PNH Phase 1 and 2 | 32.7 | | | (30.7; 34.6) |
| 7 RE PNH Phase 3 | 16.3 | | | (15.7; 16.9) |
| **IIV (CV%)** | | | | |
| ETA1 – CL | 20.2 | | | (18.2; 22.1) |
| ρ(ETA1-CL, ETA2-V2) | 0.575 | | | - |
| ETA2 – V2 | 21.0 | | | (18.3; 23.5) |
| ETA3 – KA | 52.3 | | | (45.9; 58.2) |
| **OFV** | -8729.925 | | | |
| **CN** | 92 | | | |

ASE = asymptotic standard error; %RSE = percent relative standard error; 95% CI = 95 percent confidence interval; TVCL = typical value of clearance; TVV2 = typical value of volume of the central compartment; TVKA = typical value of first-order absorption rate constant; F1 = subcutaneous bioavailability; PNH =

A comparison of VPC plots for Phase 3 studies generated using the final updated model and the sensitivity analysis model was performed. These plots demonstrate a trade-off between predictive ability for Study APL2-302 and Study APL2-308 when adding a study effect covariate for the latter study. While the addition of a study effect for Study APL2-308 improves the predictions in that study, it results in a worsening of fit for Study APL2-302.

The ratio of steady-state Cavg for Study APL2-308 relative to other PNH patient studies is predicted to be 1.20 (90% CI, 1.12-1.28), which indicates higher exposure for this study but with uncertainty (90% CI) overlapping the reference interval of 0.8 to 1.25. This difference in exposure is unlikely to be clinically meaningful.




The red circles show the median ratio of the exposure metric under the test conditions compared to the reference. The blue line segments represent the corresponding 90% confidence interval. The reference condition was a PNH patient with body weight of 70 kg. Vertical dashed lines indicate the reference interval of 0.8-1.25.

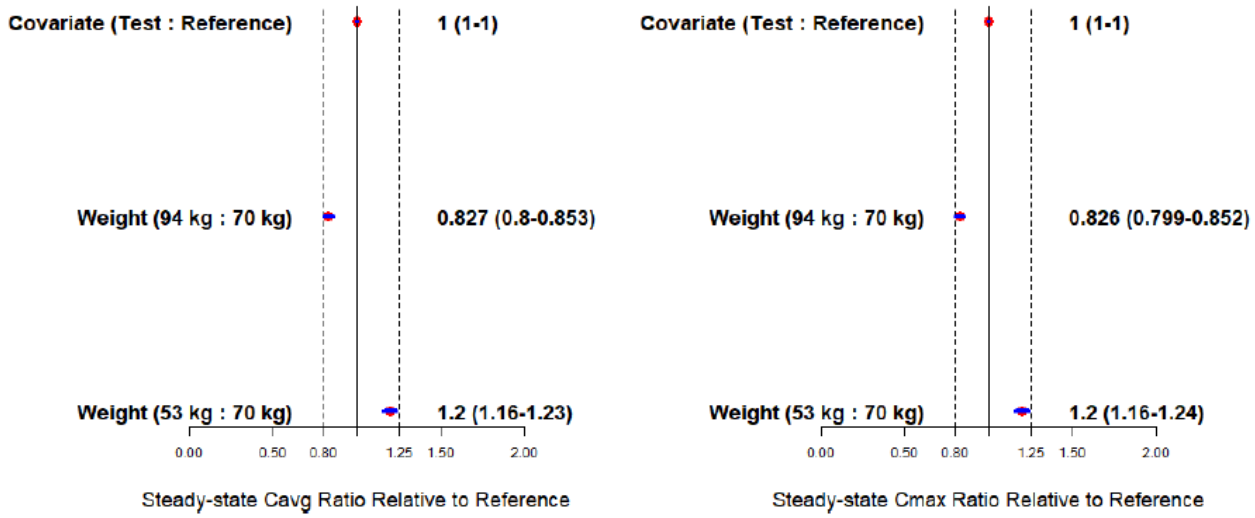
Cavg = average drug concentration over one week

Note: Simulations (N=1000) were performed for virtual subjects (one per test condition and reference), with parameter uncertainty incorporated using a smoothed parametric bootstrapping procedure based on the updated final model parameter estimates.

**Figure 3: Forest Plot for the Sensitivity Analysis of Study APL2-308 on Cavg**

*Impact of weight*

The impact of weight on pegcetacoplan exposure metrics (steady-state average concentration (Cavg) and Cmax) were evaluated by using model-based simulations. The results are presented in forest plots below. Overall, the 90% CIs of the test:reference ratios for the effect of body weight fell within or overlapped the 0.8-1.25 reference range for both Cavg and Cmax, suggesting no clinically meaningful impact on pegcetacoplan exposure.




The red circles show the median ratio of the exposure metric under the test conditions compared to the reference. The blue line segments represent the corresponding 90% confidence interval. The reference condition was a PNH patient with body weight of 70 kg. Vertical dashed lines indicate the reference interval of 0.8-1.25.

Cavg = average pegcetacoplan concentration over one week; Cmax = maximum (peak) pegcetacoplan concentration over one week

Note: Simulations (N=1000) were performed for virtual subjects (one per test condition and reference), with parameter uncertainty incorporated using a smoothed parametric bootstrapping procedure based on the updated final model parameter estimates.

**Figure 4: Influence of Covariates on Predicted Pegcetacoplan Steady-state Cavg and Cmax**

Pegcetacoplan CL is predicted to be approximately within 20% of the reference value for a 70 kg subject over the 5th (53 kg) to the 95th (94 kg) percentiles of baseline body weight (shaded region).

**Table 10: Simulation of steady state exposure for fixed body weight values**

| Weight (kg) | Percentiles of Exposure Parameters | | | | | |
|---|---|---|---|---|---|---|
| | 5th | 25th | 50th | 75th | 95th | Median Fold Change |
| | | | Cmax,ss (µg/mL) | | | |
| 40 | 711 | 873 | 1001 | 1134 | 1390 | 1.46 |
| 50 | 616 | 743 | 834 | 967 | 1173 | 1.22 |
| 60 | 554 | 668 | 773 | 878 | 1061 | 1.13 |
| 70 | 492 | 593 | 684 | 782 | 951 | 1.00 |
| 80 | 453 | 553 | 633 | 730 | 869 | 0.925 |
| 90 | 408 | 501 | 587 | 679 | 823 | 0.859 |
| 100 | 390 | 467 | 538 | 621 | 755 | 0.786 |
| 110 | 362 | 442 | 514 | 590 | 726 | 0.751 |
| 120 | 346 | 420 | 489 | 558 | 685 | 0.715 |
| 130 | 332 | 407 | 465 | 531 | 665 | 0.681 |
| 140 | 311 | 378 | 434 | 507 | 611 | 0.635 |
| 150 | 299 | 364 | 420 | 486 | 592 | 0.614 |
| 160 | 291 | 346 | 399 | 467 | 567 | 0.584 |
| | | | Cavg,ss (µg/mL) | | | |
| 40 | 673 | 833 | 960 | 1096 | 1338 | 1.45 |
| 50 | 594 | 706 | 807 | 927 | 1146 | 1.22 |
| 60 | 533 | 647 | 744 | 849 | 1038 | 1.12 |
| 70 | 471 | 574 | 665 | 752 | 921 | 1.00 |
| 80 | 434 | 530 | 613 | 706 | 844 | 0.923 |
| 90 | 395 | 482 | 567 | 654 | 798 | 0.854 |
| 100 | 377 | 452 | 521 | 600 | 737 | 0.784 |
| 110 | 349 | 427 | 495 | 572 | 702 | 0.745 |
| 120 | 335 | 408 | 473 | 544 | 665 | 0.712 |
| 130 | 315 | 393 | 452 | 517 | 646 | 0.680 |
| 140 | 302 | 366 | 419 | 492 | 591 | 0.631 |
| 150 | 290 | 352 | 409 | 471 | 573 | 0.616 |
| 160 | 280 | 335 | 387 | 454 | 554 | 0.583 |

Cavg,ss = average concentration at steady-state; Cmax,ss = peak (maximum) concentration at steady-state

Model-based simulations of steady-state exposures (Cmax and Cavg) were performed in fixed body weight values in increments of 10 kg covering the approximate range of baseline body weights in the dataset. In the simulation, parameters were fixed to their estimated values from the final updated model and used to generate 1000 simulated subjects at each body weight.

*Simulation of dosing regimen*

Various SC dosing regimens were simulated reflecting those used in patient studies during the clinical development of pegcetacoplan: 270 mg once daily, 360 mg once daily, 1080 mg twice weekly, and 1080 mg every three days. A total of 1000 simulated subjects were generated for each dosing regimen and exposure measures were derived from simulated concentration-time profiles with rich sampling at weeks 1 and 16, and individual clearance (CL) and central volume of distribution (V2) estimates were generated and summarized.

**Table 11: Predicted Pharmacokinetic Parameters in Healthy Subjects and PNH Patients Receiving Pegcetacoplan 1080 mg**

| Population | Summary Statistic | CL (L/hr) | CL (L/day) | V2 (L) | $t_{½,eff}$ (days) |
|---|---|---|---|---|---|
| Healthy Subjects | Mean (SD) | 0.0122 (0.00278) | 0.293 (0.0667) | 4.15 (0.990) | 12.5 (5.80) |
| | Geometric Mean (%CV) | 0.0119 (25.2%) | 0.286 (25.2%) | 4.04 (26.7%) | 11.6 (45.8%) |
| | Median | 0.0119 | 0.285 | 4.05 | 11.0 |
| | (IQR) | (0.0103 - 0.0139) | (0.246 - 0.334) | (3.42 - 4.72) | (8.70 - 14.2) |
| | 5th; 95th Percentile | 0.00823; 0.0174 | 0.198; 0.417 | 2.78; 5.95 | 7.00; 24.7 |
| PNH Patients | Mean (SD) | 0.0153 (0.00412) | 0.368 (0.0990) | 4.14 (1.24) | 9.60 (4.20) |
| | Geometric Mean (%CV) | 0.0148 (29.5%) | 0.356 (29.5%) | 3.98 (32.4%) | 9.00 (43.4%) |
| | Median | 0.0146 | 0.351 | 3.95 | 8.60 |
| | (IQR) | (0.0125 - 0.0177) | (0.299 - 0.424) | (3.27 - 4.79) | (6.90 - 11.0) |
| | 5th; 95th Percentile | 0.00980; 0.0230 | 0.235; 0.553 | 2.56; 6.34 | 5.40; 17.5 |

CL = systemic pegcetacoplan clearance; V2 = central volume of distribution; $t_{½,eff}$ = effective half-life; SD = standard deviation; %CV = percent coefficient of variation; IQR = interquartile range

Exposures for the different regimen in patients and healthy subjects can be found below.

**Table 12: Predicted Steady-state Pharmacokinetic Exposure Measures in Healthy Subjects and PNH Patients Receiving Various Pegcetacoplan Dosing Regimens**

| | Healthy Subjects | | | PNH Patients | | |
|---|---|---|---|---|---|---|
| **Dose Regimen and Summary Statistic** | **Cmax,ss (µg/mL)** | **AUCweek,ss (µg·hr/mL)** | **Cavg,ss (µg/mL)** | **Cmax,ss (µg/mL)** | **AUCweek,ss (µg·hr/mL)** | **Cavg,ss (µg/mL)** |
| **270 mg once daily** | | | | | | |
| Mean (SD) | 738 (174) | 123933 (29195) | 738 (174) | 591 (146) | 99199 (24571) | 591 (146) |
| Geometric Mean (%CV) | 719 (26.3%) | 120618 (26.3%) | 718 (26.3%) | 573 (28.1%) | 96232 (28.1%) | 573 (28.1%) |
| Median | 715 | 120065 | 715 | 575 | 96469 | 574 |
| (IQR) | (621 - 839) | (104261 - 140745) | (621 - 838) | (488 - 678) | (81883 - 113767) | (487 - 677) |
| 5th, 95th Percentile | 491; 1057 | 82373; 177266 | 490; 1055 | 381; 847 | 64000; 142178 | 381; 846 |
| **360 mg once daily** | | | | | | |
| Mean (SD) | 985 (232) | 165244 (38927) | 984 (232) | 788 (195) | 132266 (32761) | 787 (195) |
| Geometric Mean (%CV) | 958 (26.3%) | 160824 (26.3%) | 957 (26.3%) | 764 (28.1%) | 128310 (28.1%) | 764 (28.1%) |
| Median | 954 | 160086 | 953 | 766 | 128626 | 766 |
| (IQR) | (828 - 1119) | (139015 - 187660) | (828 - 1117) | (651 - 903) | (109177 - 151689) | (650 - 903) |
| 5th, 95th Percentile | 654; 1409 | 109831; 236354 | 654; 1407 | 508; 1129 | 85333; 189570 | 508; 1128 |
| **1080 mg twice weekly** | | | | | | |
| Mean (SD) | 861 (193) | 140671 (31742) | 837 (189) | 704 (180) | 113993 (29181) | 679 (174) |
| Geometric Mean (%CV) | 840 (24.9%) | 137194 (25.1%) | 817 (25.1%) | 682 (29.4%) | 110323 (29.4%) | 657 (29.4%) |
| Median | 840 | 137318 | 817 | 693 | 112002 | 667 |
| (IQR) | (722 - 972) | (117661 - 159294) | (700 - 948) | (573 - 813) | (92636 - 131322) | (551 - 782) |
| 5th, 95th Percentile | 579; 1207 | 94285; 198272 | 561; 1180 | 435; 1027 | 71048; 166956 | 423; 994 |
| **1080 mg every 3 days** | | | | | | |
| Mean (SD) | 995 (234) | 165062 (38909) | 983 (232) | 799 (197) | 132069 (32727) | 786 (195) |
| Geometric Mean (%CV) | 969 (26.2%) | 160641 (26.3%) | 956 (26.3%) | 775 (28.1%) | 128116 (28.1%) | 763 (28.1%) |
| Median | 963 | 159829 | 951 | 778 | 128317 | 764 |
| (IQR) | (837 - 1135) | (138900 - 187549) | (827 - 1116) | (659 - 916) | (109000 - 151487) | (649 - 902) |
| 5th, 95th Percentile | 660; 1417 | 109758; 236172 | 653; 1406 | 515; 1142 | 85124; 189297 | 507; 1127 |

$C_{max,ss}$ = maximum (peak) concentration at steady-state; $AUC_{week,ss}$ = area under the concentration-time curve over a week at steady-state; $C_{avg,ss}$ = average concentration at steady-state; SD = standard deviation; %CV = percent coefficient of variation; IQR = interquartile range

In summary, a population PK model including 1-compartment disposition, transit compartment absorption via the SC route, IV administration directly into the central compartment, and first order elimination, which adequately described the serum concentration-time profile of pegcetacoplan in healthy adults, adults with renal impairment, and adult patients with PNH, was updated with new data from Phase 3 studies.

The following conclusions are drawn from the updated population PK model for pegcetacoplan:

- SC bioavailability was estimated as 75.8% for liquid formulations; higher bioavailability is estimated for the lyophilized formulation (92.5%).

- Patients with PNH are predicted to have lower pegcetacoplan exposure than healthy subjects due to increased systemic clearance. The median effective half-life of pegcetacoplan at a subcutaneous dose of 1080 mg twice weekly was estimated as 8.6 days for adult PNH patients compared and 11 days for healthy adults.

• Baseline body weight was a significant covariate of both pegcetacoplan clearance and volume of distribution. Both clearance and volume of distribution increase nonlinearly with increasing body weight, leading to lower predicted pegcetacoplan exposure at higher body weights. Compared with a reference 70-kg subject, weekly Cmax,ss and Cavg,ss are predicted to be approximately 20% higher in subjects at the 5th percentile of body weight (53 kg) and 17% lower in subjects at the 95th percentile of body weight (95 kg).

• Age, sex, Asian race, baseline CrCl, baseline total bilirubin, baseline albumin, baseline AST, and baseline ALT, and eculizumab coadministration had no statistically significant impact on the PK parameters of pegcetacoplan.

## *Absorption*

Evaluation of the PK properties of pegcetacoplan across healthy subjects where only a single dose was given shows that following a single SC dose of pegcetacoplan, absorption is slow with a geometric mean Tmax that ranges between 4.5 to 6 days (108 to 144 hours).

In the pegcetacoplan group of Study APL2-308, serum pegcetacoplan concentrations reached a steady-state level between Week 4 and Week 12, and steady state was sustained through Week 26. The geometric mean (coefficient of variation [CV]) drug concentration at Week 26 was 744 µg/mL (25.5%) with twice-weekly dosing. Treatment duration for subjects in the SoC-to-pegcetacoplan group in this study was not uniform because the timing for patients to escape SoC treatment varied. However, most of the subjects had either reached or approximated the steady-state drug exposure level at Week 26. The geometric mean (CV) drug concentration at Week 26 was 809 µg/mL (17.7%), which was similar to that observed for the pegcetacoplan group.

**Table 13: Exposure in Study APL2-308**

| | | Parameter: Pegcetacoplan (µg/mL) | | |
|---|---|---|---|---|
| | | Pegcetacoplan | | |
| Analysis Visit | Statistics | Pegcetacoplan (N=35) | SOC to Pegcetacoplan (N=11) | Overall (N=46) |
| Week 20 | n | 30 | 10 | 40 |
| | Mean (SD) | 801.8 (161.57) | 752.8 (280.05) | 789.6 (194.86) |
| | CV | 20.15 | 37.20 | 24.68 |
| | Q1, Q3 | 672, 938 | 781, 873 | 687, 921 |
| | Min, Max | 516, 1130 | 0, 995 | 0, 1130 |
| | Geo Mean (CV %) | 785.7 (20.9) | 831.4 (11.8) | 796.0 (19.2) |
| Week 26 | n | 27 | 9 | 36 |
| | Mean (SD) | 766.9 (190.64) | 819.6 (124.68) | 780.1 (176.31) |
| | CV | 24.86 | 15.21 | 22.60 |
| | Q1, Q3 | 620, 904 | 804, 902 | 652, 902 |
| | Min, Max | 428, 1150 | 524, 966 | 428, 1150 |
| | Geo Mean (CV %) | 744.3 (25.5) | 809.4 (17.7) | 760.1 (23.8) |

- Formulation Evaluation by PopPK Analysis

A PopPK analysis (APL-EX20-CP-002) was completed for pegcetacoplan using the data from 10 Phase 1 through Phase 3 studies, including those completed in healthy subjects, subjects with renal impairment, and subjects with PNH. This analysis was updated to incorporate the additional data from the OLP of Study APL2-302, up to Week 48 and the results of Study APL2-308 but with no further structural changes to the model (APL-EX21-CP-010). Pegcetacoplan PK following SC or IV administration was adequately described by a 1- compartment model with transit compartment absorption for SC administration and first-order elimination.

SC bioavailability was assessed as part of the PopPK analysis. It was estimated that bioavailability was 75.8% for the sorbitol, mannitol, and dextrose formulations, whereas higher bioavailability was estimated for the lyophilized drug substance formulation (92.5%).

These estimates are in general agreement with those determined from cross-study comparison using dose-normalized AUC0-∞ and indicate that SC pegcetacoplan is well absorbed.

## *Distribution*

No changes in this section (see results in Table 8).

## *Elimination*

PK properties of pegcetacoplan were further assessed in another multiple-dose study, Study APL2-101, to evaluate SC dosing regimen of 360 mg daily (4 weeks), 1080 mg twice weekly (4 weeks), 1300 mg twice weekly (4 weeks), and 2600 once weekly (4 weeks). Geometric mean of half-life was in the range of 206.1 to 243.8 hours (8.6 to 10.2 days) with CV ≤15% across cohorts.

The CL/F values for pegcetacoplan in healthy subjects appear to be generally consistent between single and multiple-dosing regimens with geometric means of 11.1 to 17.2 mL/h and 15.7 to 20.7 mL/h, respectively. Although in the single-dose study the CL/F was highest at the lowest dose of 45 mg (17.2 mL/h), there did not appear to be any relationship between dose and CL/F following repeated dosing for 4 weeks, indicating that pegcetacoplan CL is not dose- or time-dependent following dosing for this time period. Median t½ values for pegcetacoplan ranged from approximately 8 to 10 days across studies, doses, and time since first dose, when an estimate could be determined.

No changes were deemed necessary in this section (see results in Table 11.).

## *Target population*

In Study APL2-302, serum pegcetacoplan concentration reached steady state approximately 4 to 6 weeks after the first dose. Mean steady-state serum concentrations ranged from 659.6 to 714.2 µg/mL. In patients receiving twice-weekly doses of pegcetacoplan in Study APL2-308, serum pegcetacoplan concentrations reached a steady-state level between Week 4 and Week 12, and which was sustained through Week 26. Mean steady-state serum concentrations ranged from 711.3 to 807.1 µg/mL. Similarly, steady-state exposure of pegcetacoplan was reached approximately 4 to 6 weeks after the first dose for both Study 204 and Study 202. In Study CP0514 (cohort 4), steady state was reached at approximately 6 to 8 weeks, although individual subjects may have reached steady state after 4 to 6 weeks of dosing.

Population PK analysis (Report APL-EX21-CP-010) demonstrated that patients with PNH are predicted to have lower pegcetacoplan exposure than healthy subjects because of increased systemic clearance. The median effective half-life of pegcetacoplan at a subcutaneous dose of 1080 mg twice weekly was estimated as 8.6 days for adult PNH patients and 11 days for healthy adults.

**Table 14: Summary of pegcegatoplan serum conentration (microg/mL) data in different studies**

| | Study APL2-302 | Study APL2-308 | Study APL2-CP-PNH-204 | Study APL-CP0514 (Cohort 4) | Study APL2-202 |
|---|---|---|---|---|---|
| | Pegcetacoplan 1080 mg twice weekly[a] N = 41 in RCP (pegcetacoplan only) N=77 in OLP (Combined OLP) µg/mL | Pegcetacoplan 1080 mg twice weekly[a] N = 35 µg/mL | Pegcetacoplan 270 mg/d[b] N = 20 µg/mL | Pegcetacoplan 270 mg/d[c] N = 6 µg/mL | Pegcetacoplan 270 mg/d[b] N = 4 µg/mL |
| **Baseline** | | | | | |
| Predose (n) | 41 | 33 | 20 | 6 | 2 |
| Mean (SD) | 10.00 (0.00) | 0.0 (0.00) | 0.0094 (0.4204) | 0.0 (0.00) | 0.40 (0.03) |
| Min, max | 10.0, 10.0 | 0, 0 | 0, 0.188 | 0, 0 | 0.38, 0.43 |
| **Day 15 (n)/ Week 2** | 41 | 32 | Not reported | 6 | Not reported |
| Mean (SD) | 665.85 (117.66) | 515.6 (118.29) | | 156.0 (57.30) | |
| Min, max | 412.0, 893.0 | 103, 737 | | 93, 248 | |
| **Day 29 (n)/ Week 4** | 40 | 29 | 20 | 6 | 4 |
| Mean (SD) | 676.23 (114.56) | 711.3 (132.07) | 518.91 (162.55) | 400.5 (155.75) | 637.25 (133.42) |
| Min, max | 374.0, 881.0 | 483, 971 | 17.10, 792.0 | 206, 655 | 488.00, 777.00 |
| **Day 43 (n)/ Week 6** | 39 | Not reported | 18 | 5 | 4 |
| Mean (SD) | 676.92 (132.36) | | 611.89 (147.75) | 556.8 (229.40) | 727.00 (146.23) |
| Min, max | 341.0, 928.0 | | 368.0, 915.0 | 262, 797 | 576.00, 901.00 |
| **Day 57 (n)/ Week 8** | 38 | Not reported | Not reported | 5[d] | Not reported |
| Mean (SD) | 692.24 (104.23) | | | 570.4 (215.66) | |
| Min, max | 430.0, 912.0 | | | 259, 772 | |
| **Day 85 (n)/ Week 12** | 38 | 28 | 17 | 6 | 4 |
| Mean (SD) | 708.42 (124.29) | 807.1 (175.29) | 618.59 (142.60) | 586.0 (201.06) | 731.75 (126.54) |
| Min, max | 354.0, 957.0 | 457, 1100 | 344.0, 816.0 | 347, 794 | 569.00, 851.00 |
| **Day 113 (n)/ Week 16** | 36 | Not reported | 20 | 6 | 4 |
| Mean (SD) | 714.19 (109.015) | | 570.25 (173.53) | 489.7 (177.73) | 754.50 (149.70) |
| Min, max | 521.0, 998.0 | | 240.0, 823.0 | 243, 712 | 596.00, 912.00 |
| **Day 141 (n)/ Week 20** | 41 | 30 | 18 | 6 | 4 |
| Mean (SD) | 674.98 (145.173) | 801.8 (161.57) | 608.94 (136.01) | 515.0 (137.31) | 711.00 (112.75) |
| Min, max | 336.0, 978.0 | 516, 1130 | 321.0, 861.0 | 289, 641 | 613.00, 864.00 |

**Table 14 (ctd): Summary of pegcegatoplan serum conentration (microg/mL) data in different studies**

| | Study APL2-302 | Study APL2-308 | Study APL2-CP-PNH-204 | Study APL-CP0514 (Cohort 4) | | | Study APL2-202 |
|---|---|---|---|---|---|---|---|
| | Pegcetacoplan 1080 mg twice weekly[a] N = 41 in RCP (pegcetacoplan only) N=77 in OLP (Combined OLP) µg/mL | Pegcetacoplan 1080 mg twice weekly[a] N = 35 µg/mL | Pegcetacoplan 270 mg/d[b] N = 20 µg/mL | Pegcetacoplan 270 mg/d[c] N = 6 µg/mL | | | Pegcetacoplan 270 mg/d[b] N = 4 µg/mL |
| **Day 169 (n)/ Week 24** | 75 | Not reported | 18 | 270 mg[e] (5) | 280 mg[e] (1) | | 4 |
| Mean (SD) | 667.17 (156.189) | | 599.06 (161.79) | 494.8 (159.23) | 634.0 (NA) | | 704.25 (131.53) |
| Min, max | 274.0, 1090.0 | | 301.0, 851.0 | 282, 684 | 634, 634 | | 602.00, 887.00 |
| **Day 183 (n)/ Week 26** | Not reported | 27 | NA | NA | | | NA |
| Mean (SD) | | 766.9 (190.64) | | | | | |
| Min, max | | 428, 1150 | | | | | |
| **Day 365 (n)/ Week 48** | 40[f] | NA | 17 | 280 mg[e] (4) | | | 4 |
| Mean (SD) | 644.73 (184.860) | | 526.24 (151.95) | 469.0 (74.97) | | | 622.00 (92.13) |
| Min, max | 179.0, 969.0 | | 200.0, 731.0 | 358, 523 | | | 512.00, 703.00 |
| **Day 729 (n)** | NA | NA | NA | 280 mg[e] (1) | 360 mg[e] (1) | 440 mg[e] (1) | NA |
| Mean (SD) | | | | 581.0 (NA) | 524.0 (NA) | 624.0 (NA) | |
| Min, max | | | | 581, 581 | 524, 524 | 624, 624 | |

Abbreviations: CFB = change from baseline; max = maximum; CSR = clinical study report; mean = arithmetic mean; min = minimum; NA = not applicable; RCP = randomized controlled period.

[a] Values are for subjects randomized to pegcetacoplan; days are relative to the start of the RCP. Dose could be increased to 1080 mg 3 times weekly if clinically indicated.

[b] Study duration was up to 365 days. Dose could be increased to 360 mg/d if clinically indicated. Subjects were naive to C5 inhibitor treatment. As described in Section 2.2.3.1, a change in formulation and a switch from daily injections to the use of a self-administration pump in Protocol Amendment 6 resulted in delivery of a nominal dose of 280 mg.

[c] Cohort 4 only. Study duration was up to 729 days (2 years). Dose could be increased to 360 mg/d if clinically indicated; one subject was granted approval to receive 360 mg/d, with a dose of 720 mg every 4th day (equivalent to approximately 440 mg/d). Subjects received pegcetacoplan as an add-on to C5 inhibitor treatment.

[d] 1 subject was not dosed.

[e] Last dose prior to draw.

[f] Week 48 (Day 336 in APL2-302)

An exposure in PBH patients lower than in healthy subjects is consistent with the exposures simulated by the applicant, and those shown in Table 12. Effects of those expected exposures on PKPD are detailed in the PKPD section.

## *Special populations*

- Race

When the PK of a single dose of SC pegcetacoplan in Japanese subjects (Study APL2-102) was compared with the PK in non-Japanese subjects (Study APL-CP0713-1), median Tmax ranging between

5.5 to 8.0 days was found to be slightly longer than healthy non-Japanese subjects (4.5 to 6.0 days). Cmax values were similar across dose groups tested. Geometric means of AUC0-∞ trended higher across dose groups for Japanese subjects (approximately 11% to 36%) than for non-Japanese subjects. However, the highest difference was observed in the low dose group (180-mg dose). Excluding the low dose group, geometric means of AUC0-∞ from Japanese subjects are approximately 11% to 17% higher than non-Japanese subjects. A slightly lower geometric mean CL/F was observed in Japanese subjects, across doses (9.8 to 12.7 mL/h) than that for non-Japanese subjects (Study APL-CP0713-1, 11.1 to 17.2 mL/h). Because these CL values also incorporate bioavailability (F), slight differences in F could factor into the slight difference seen in CL/F between these 2 populations. Geometric mean of Vz/F (2.9 to 4.0 L) observed in Japanese subjects was generally consistent with those from non-Japanese subjects (3.6 to 4.8 L). The median t½ in Japanese subjects (8.8 to 10.2 days) was also similar to those from non-Japanese subjects (Study APL-CP0713-1, 8.1 to 9.6 days).

The data suggested there was no meaningful differences in the PK of pegcetacoplan between Japanese and non-Japanese subjects at single SC doses above 180 mg. This is further supported by PopPK analysis ( Report APL-EX21-CP-010), which demonstrated that Japanese ethnicity had no significant impact on the PK of pegcetacoplan.

- Renal impairment

Although renal excretion was the primary route of pegcetacoplan elimination in monkeys (Module 2.6.4), renal impairment does not appear to impact the SC PK of pegcetacoplan (Study APL2-CP-PV-205) in human subjects. When exposure metrics for subjects with severe renal impairment and a group of sex, age, and weight-matched healthy subjects were compared, severe/control ratios for geometric mean values were approximately 91.5% to 100% of each other. The data from Study APL2-CP-PV-205 indicate that there is no meaningful difference in pegcetacoplan PK between those with severe renal impairment and healthy matched-control subjects. This is further supported by PopPK analysis (Report APL-EX21-CP-010), which demonstrates that baseline CrCl from healthy subjects and PNH subjects had no significant impact on the PK of pegcetacoplan.

- Influence of body weight

Table 10 displays that exposure will increase roughly by 22% for patients weighting 50 kg, and by 45% for patients weighting 40 kg.

- Anti-Pegcetacoplan Peptide Antibody

In Study APL2-308, 1 of the 46 subjects in the pegcetacoplan treatment group (2.2%) had a positive anti-pegcetacoplan peptide antibody response in a sample collected on Day 1, prior to dosing. This subject received only 1 dose of pegcetacoplan and then was lost to follow-up. No other subjects in either treatment group tested positive for anti-pegcetacoplan peptide antibodies during the study.

- Anti-PEG Antibody

In Study APL2-308, 7 of the 46 subjects (15.2%) who received at least 1 dose of pegcetacoplan were considered to have treatment-emergent responses for anti-PEG antibody, and 5 of the 46 subjects (10.9%) were considered to have developed treatment-boosted responses.

## 2.3.3. Pharmacodynamics

Pharmacodynamics endpoints

- Change from baseline to Week 26 in PNH clone distribution (RBCs and white blood cells [WBCs])
- Change from baseline to Week 26 in C3 deposition on PNH Type II and III RBCs

- Complement concentrations (total haemolytic complement activity assay [CH50], alternative pathway haemolytic complement assay [AH50], and C3) from baseline to Week 26

The PD endpoints were evaluated using the PD set.

The PD set included all subjects in the ITT set who had at least 1 evaluable post-dose PD measurement.

Absolute values, changes from baseline, and percent changes from baseline were summarized using descriptive statistics over time in CSR section 11.5.

PD related to PNH RBCs, PNH Types II and III and RBCs with C3 deposition, percent of fluorescent aerosylin (FLAER) for observed for PNH granulocytes or PNH monocytes was assessed by flow cytometry at Week 26 (CSR, section 11.5.1). PD through complement markers (C3, AH50, CH50) was also explored (CSR, section 11.5.2)

Individual subject-time profiles were plotted against actual sampling time. Median profiles over time, using nominal sampling time, were also presented.

The PD endpoints for the treatment groups were compared using MMRM analyses.

### 2.3.4. PK/PD modelling

PKPD modelling is presented by the applicant in report APL-EX21-CP-011.

- Exposure Relationship to Hemoglobin Response in Subjects With PNH

An existing sigmoidal Emax direct effect model for Hb response to pegcetacoplan concentration was updated using dosing information and Hb data from 5 clinical studies in patients with PNH (two Phase 1b studies, one Phase 2a study, and two Phase 3 studies). A total of 165 patients with 3142 Hb samples were included in the E-R analysis.

**Table 15: E-R parameter estimates for hemoglobin final updated model**

| Theta/parameter (units) | Estimate [transformed estimate[a]] | ASE | %RSE | 95% CI [transformed 95% CI[a]] |
|---|---|---|---|---|
| 1 BaseHb (g/dL) | 8.74 | 0.0950 | 1.09 | (8.55-8.93) |
| 2 Emax | 0.510 | 0.0402 | 7.88 | (0.431-0.589) |
| 3 EC50 (µg/mL) | 337 | 17.9 | 5.30 | (302-372) |
| 4 Hill | 4.66 | 0.435 | 9.33 | (3.81-5.52) |
| 6 CrCl on Emax | 0.641 | 0.106 | 16.6 | (0.433-0.850) |
| 7 Female sex on Emax | –0.337 | 0.0609 | 18.0 | (–0.457 to –0.218) |
| **Residual variability** | | | | |
| 5 RE Additive (g/dL) | 0.913 | | | (0.888-0.938) |
| **IIV** | | | | |
| $\omega_{1,1}^2$ BaseHb | 0.0162 [12.8% CV] | | | (0.0119-0.0204) [10.9% CV-14.4% CV] |
| $\omega_{2,1}$ Emax:BaseHb | –0.0437 [ρ = –0.580] | | | – |
| $\omega_{2,2}^2$ Emax | 0.351 [64.8% CV] | | | (0.239-0.463) [52.0% CV-76.7% CV] |
| $\omega_{3,3}^2$ EC50 | 0.291 [58.1% CV] | | | (0.201-0.381) [47.2% CV-68.1% CV] |
| **CN** | **16.1** | | | |

Abbreviations: %RSE = percentage relative standard error; ASE = asymptotic standard error; BaseHb = population estimate of baseline hemoglobin level; BECU = baseline eculizumab; CN = condition number; CrCl = creatinine clearance calculated using the Cockcroft-Gault equation; CV = coefficient of variation; EC50 = pegcetacoplan concentration eliciting 50% of maximal effect; Emax = maximum proportional drug effect; Hill = sigmoidicity coefficient; IIV = interindividual variability; RE = residual error.

[a] CV calculated as $\left(\sqrt{\exp(\omega^2)-1}\right)\cdot 100\%$. η-shrinkage: 7.7% ($\eta_1^{BaseHb}$), 15.2% ($\eta_2^{Emax}$), 19.7% ($\eta_3^{EC50}$).

Notes: The following equations describe the covariate-parameter relationships in the model:

$$Hb_i = BaseHb_i \cdot \left(1 + \frac{Emax_i \cdot C_t^{Hill}}{EC50_i^{Hill} + C_t^{Hill}}\right)$$

$$BaseHb_i = TVBaseHb \cdot exp(\eta_i^{BaseHb})$$

$$Emax_i = TVEmax \cdot \left(\frac{CrCl_i}{120}\right)^{\theta_6} \cdot (1 + SEXF \cdot \theta_7) \cdot exp(\eta_i^{Emax})$$

$$EC50_i = TVEC50 \cdot exp(\eta_i^{EC50})$$

where parameters are defined as follows:

- $Hb_i$ is the hemoglobin level for the $i^{th}$ subject at a given pegcetacoplan concentration at time $t$ ($C_t$).
- $BaseHb_i$ is the model-estimated baseline hemoglobin level for the $i^{th}$ subject, $TVBaseHb$ ($\theta_1$) is the typical value of baseline hemoglobin level in the population; $\eta_i^{BaseHb}$ is the $i^{th}$ individual's deviation from the population baseline hemoglobin.
- $Emax_i$ is the maximal proportional CFB in hemoglobin level with pegcetacoplan concentration for the $i^{th}$ subject, $TVEmax$ ($\theta_2$) is the typical value of Emax in the population; $\eta_i^{Emax}$ is the $i^{th}$ individual's deviation from the population maximal effect.
- $\theta_6$ is the power describing the relationship between baseline creatinine clearance for the $i^{th}$ subject ($CrCl_i$) and Emax centered on the approximate median baseline CrCl of 120 mL/min.
- $\theta_7$ is the proportional shift in Emax for female sex (SEXF=1) relative to male sex (SEXF=0).
- $EC50_i$ ($\theta_4$) is the pegcetacoplan concentration at which 50% of the maximal effect is reached for the $i^{th}$ subject, $TVEC50$ ($\theta_5$) is the typical value of EC50 in the population; $\eta_i^{EC50}$ is the $i^{th}$ individual's deviation from the population EC50.
- $Hill$ ($\theta_4$) is the coefficient describing the sigmoidicity of the relationship between Hb level and pegcetacoplan concentration.

Source: Report APL-EX21-CP-011, Table 15.

The typical subject (defined by the population fixed effect parameters) was predicted to have an Emax of 0.510 (ie, maximum 51.0% increase from baseline in Hb) and an EC50 of 337 µg/mL. The pegcetacoplan concentration-Hb response relationship was steep over the observed pegcetacoplan concentration range with a Hill coefficient of 4.66. Interindividual variation baseline Hb and Emax was negatively correlated (ρ = –0.580), such that individuals with lower baseline Hb concentration have a greater proportional increase in Hb concentration with pegcetacoplan treatment.

Covariate Effects on Hb Response

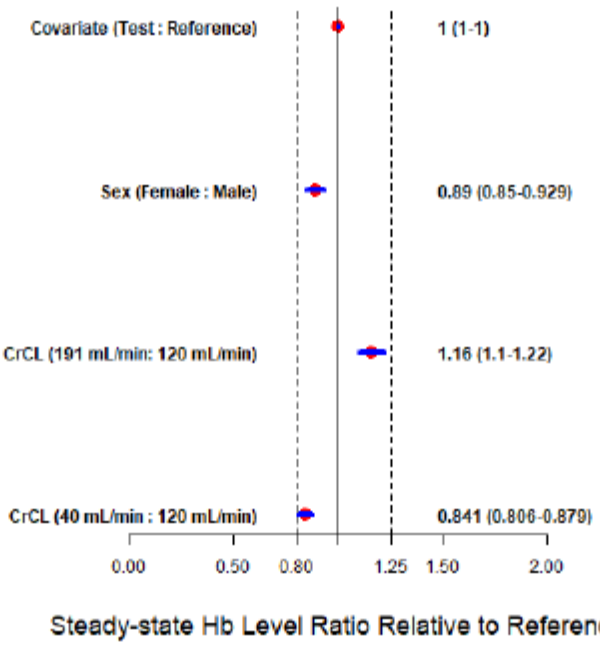
Female sex is associated with a decrease in Emax, such that Emax decreases to 0.338 (ie, 33.8% increase from baseline Hb) for women compared with men at the reference CrCl of 120 mL/min. Lower CrCl is also associated with a decrease in Emax, such that at the 5th percentile of CrCl (40 mL/min),

Emax decreases to 0.252 (ie, 25.2% increase from baseline Hb) compared with the typical male individual with the median CrCl of 120 mL/min.

Model-based simulations were performed to assess the impact of covariates on predicted Hb. Steady-state Hb levels were simulated for virtual subjects differing only in specific test conditions relative to reference conditions.

Steady-state Hb level was determined as the average across the predicted values over a 1-week interval at steady state following pegcetacoplan 1080 mg SC twice weekly. The population-predicted Hb level ratios (test:reference) and 90% CIs were calculated for each comparison and presented in a forest plot. Results are illustrated in Figure below. Overall, the 90% CI for all covariates fell within the 0.8-1.25 reference range, indicating that none of these factors are anticipated to have meaningful effects on the E-R relationship between pegcetacoplan concentration and Hb.

Other intrinsic subject factors evaluated as covariates of E-R parameters included Asian race, age, body weight, baseline eculizumab treatment status, and baseline C3 level. None of these factors are anticipated to have meaningful effects on the E-R relationship between pegcetacoplan concentration and Hb.




Abbreviations: CrCL = creatinine clearance; Hb = hemoglobin.
Note: Red circles show the Hb level ratio under the test conditions compared to the reference over a week at steady state following administration of the sorbitol formulation of pegcetacoplan 1080 mg subcutaneously twice weekly.
The horizontal blue lines represent the corresponding 90% CI. Reference conditions for continuous covariates are the approximate median in the population. Test conditions for categorical covariates were the alternative category, and test conditions for the continuous covariates include the 5th and 95th percentiles among subjects in the analysis data set.
Vertical dashed lines indicate a reference interval of 0.8-1.25. Simulations (N = 1000) were performed for virtual subjects (one per test condition and reference), with parameter uncertainty incorporated using a smoothed parametric bootstrapping procedure based on the final updated model parameter estimates.
Source: Report APL-EX21-CP-011, Figure 12.

**Figure 5: Influence of covariates on predicted haemoglobin level with 90% CI**

Simulations were performed using the PK and Hb E-R models to determine the predicted Hb response with pegcetacoplan 1080 mg SC twice weekly or every 3 days. In the simulation, complete covariate vectors were sampled with replacement for stationary covariates from adult patients with PNH in the modeling data set to generate 1000 virtual subjects. The median (5th, 95th percentile) average pegcetacoplan concentration (Cavg,ss) was determined from 1000 simulated patients to provide

reference exposure for assessment of Hb response under each dosing condition of interest. Additionally, average steady-state Hb concentration was predicted simultaneously and the proportion of subjects exceeding a threshold value of 12 g/dL was determined.

The relationship between pegcetacoplan exposure at doses of 1080 mg SC twice weekly or every 3 days and maximum Hb response is described by the ratio of predicted pegcetacoplan Cavg,ss to different final E-R model–predicted effect concentration thresholds and summarized in Table below.

The median steady-state pegcetacoplan Cavg,ss twice weekly dosing (667 µg/mL) is predicted to achieve at least 95% of the maximal Hb response, irrespective of prior complement inhibitor treatment. The median predicted Hb at steady-state with twice weekly dosing is 12.3 g/dL for males and 11.2 g/dL for females, with approximately 44% of all patients (54.3% of males, 33.5% of females) achieving Hb above 12 g/dL. This response appears to be durable and consistent through a year of follow up in Study APL2-302.

**Table 16: Model-predicted pegcetacoplan concentration and haemoglobin response**

| Dosing regimen | Median $C_{avg,ss}$ (µg/mL) | Effect level | Pegcetacoplan concentration (µg/mL) | Ratio of median $C_{avg,ss}$ to concentration at the effect level |
|---|---|---|---|---|
| 1080 mg SC twice weekly | 667[a] | $EC_{50}$ | 337 | 1.98 |
| | | $EC_{80}$ | 454 | 1.47 |
| | | $EC_{90}$ | 540 | 1.23 |
| | | $EC_{95}$ | 634 | 1.05 |
| | | $EC_{99}$ | 903 | 0.74 |
| 1080 mg SC every 3 days | 766[a] | $EC_{50}$ | 337 | 2.27 |
| | | $EC_{80}$ | 454 | 1.69 |
| | | $EC_{90}$ | 540 | 1.42 |
| | | $EC_{95}$ | 634 | 1.21 |
| | | $EC_{99}$ | 903 | 0.85 |

Abbreviations: $C_{avg,ss}$ = average pegcetacoplan serum concentration at steady state; $EC_{nn}$ = concentration producing nn% of the maximal response; E-R = exposure-response; Hb = hemoglobin; PK = pharmacokinetics; SC = subcutaneous.
[a] Pegcetacoplan concentration and Hb level predictions were generated in sequential simulations based on the updated PK and Hb E-R models. Virtual subjects were generated by sampling 1000 covariate vectors with replacement from the observed data set. Individual PK parameter estimates were simulated using the updated PK model and appended to the simulation data set input into the Hb E-R model.
Source: Report APL-EX21-CP-011, Table 18.

In conclusion,

• The relationship between pegcetacoplan exposure and increase in Hb level was adequately described using a sigmoidal Emax direct effect model. The maximal effect (Emax) was a 51.0% increase from baseline with an EC50 of 337 µg/mL.

• The Hb E-R model supports the conclusion that that the dosing regimen of 1080 mg twice weekly is an effective dose for Hb response in both complement inhibitor–naive patients and patients switching from C5 inhibitor therapy. The median steady-state pegcetacoplan serum concentration of 667 µg/mL associated with this dosing regimen is expected to achieve at least 95% of the maximal predicted Hb concentration increase from baseline (Emax).

• There is a relationship between baseline Hb concentration and Emax. Interindividual variation in these model parameters was negatively correlated (ρ = –0.580), such that individuals with lower baseline Hb concentration have a greater proportional increase in Hb concentration with pegcetacoplan treatment.

• Baseline creatinine clearance had an effect on Emax; however, the magnitude of difference is not anticipated to be meaningful. Steady-state Hb concentration is predicted to be 0.841-fold (90% CI, 0.806-0.879) lower at the 5th percentile of baseline creatinine clearance (40 mL/min) and 1.16-fold (90% CI, 1.10-1.22) higher at the 95th percentile (191 mL/min) relative to the approximate median baseline creatinine clearance of 120 mL/min.

• Sex had an effect on Emax; however, the magnitude of difference is not anticipated to be meaningful. Steady-state Hb concentrations are predicted to be 0.890-fold (90% CI, 0.850-0.929) lower in women than in men without a quantifiable difference in baseline Hb level.

• Asian race, age, body weight, baseline eculizumab treatment status, and baseline C3 level are not anticipated to have meaningful effects on the Hb response to pegcetacoplan.

- Exposure Relationship to Lactate Dehydrogenase Response in Subjects With PNH

An existing sigmoidal Emax direct effect model for LDH response to pegcetacoplan concentration was updated using dosing information and LDH data from 5 clinical studies in patients with PNH (two Phase 1b studies, one Phase 2a study, and two Phase 3 studies). A total of 165 patients with 3202 LDH samples were included in the E-R analysis.

**Table 17: E-R parameter estimates for LDH final updated model**

| Theta/Parameter (Units) | Estimate | ASE | %RSE | 95% CI | Transformed estimate[a] | Transformed 95% CI[a] |
|---|---|---|---|---|---|---|
| 1 Log BaseLDH (IU/L) | 7.56 | 0.0539 | 0.712 | (7.46-7.67) | 1920 | (1740-2140) |
| 2 Log BaseLDH BECU (IU/L) | 5.52 | 0.0477 | 0.865 | (5.42-5.61) | 249 | (226-273) |
| 3 Logit Emax | 2.40 | 0.117 | 4.85 | (2.17-2.63) | 0.917 | (0.898-0.933) |
| 4 Logit Emax BECU | –1.39 | 0.135 | 9.70 | (–1.65 to –1.12) | 0.200 | (0.161-0.246) |
| 5 Log EC50 (µg/mL) | 5.23 | 0.0614 | 1.17 | (5.11-5.35) | 187 | (166-211) |
| 6 Hill | 3.42 | 0.296 | 8.65 | (2.84-4.00) | – | – |
| 8 Eculizumab cotreatment on logit Emax | 0.783 | 0.0907 | 11.6 | (0.605-0.961) | – | – |
| **Residual variability** | | | | | | |
| 7 Log additive | 0.305 | 0.00406 | 1.33 | (0.297-0.313) | 30.5% | (29.7%; 31.3%) |
| **IIV** | | | | | | |
| $\omega_{1,1}^2$ BaseLDH | 0.182 | | | (0.138-0.226) | 44.7% CV | (38.5% CV; 50.4% CV) |
| $\omega_{2,1}$ Emax:BaseLDH | 0.265 | | | (0.185-0.344) | 0.719 | – |
| $\omega_{2,2}^2$ Emax | 0.745 | | | (0.506-0.983) | – | – |
| $\omega_{3,2}$ EC50:Emax | 0.167 | | | (0.0903-0.244) | 0.556 | – |
| $\omega_{3,3}^2$ EC50 | 0.121 | | | (0.0616-0.181) | 35.9% CV | (25.2% CV; 44.5% CV) |
| **CN** | **196** | | | | | |

Abbreviations: %RSE = percentage relative standard error; ASE = asymptotic standard error; BaseLDH = population estimate of baseline lactate dehydrogenase level; BECU = baseline eculizumab; CN = condition number; CV = approximate coefficient of variation; EC50 = pegcetacoplan concentration eliciting 50% of maximal effect; Emax = maximum proportional drug effect; Hill = sigmoidicity coefficient; IIV = interindividual variability; RE = residual error.

[a] Transformations are calculated as the exponentiation of the estimate for log-transformed parameters, the anti-logit of the estimate for logit transformed parameters, CV calculated as $\left(\sqrt{\exp(\omega^2)-1}\right)\cdot 100\%$ for log-normal IIV parameters, and the correlation coefficient for off-diagonal IIV parameters. η-shrinkage: 5.4% ($\eta_1^{BaseLDH}$), 17.5% ($\eta_2^{Emax}$), 30.3% ($\eta_3^{EC50}$).

Notes: Covariate effects were evaluated using centered additive parameterizations for continuous covariates and additive parameterizations for categorical covariates on the transformed scale. The following equations describe the structural covariate-parameter relationships in the model:

$$LDH_i = BaseLDH_i \cdot \left(1 - \frac{Emax_i \cdot C_i^{Hill}}{EC50_i^{Hill} + C_i^{Hill}}\right)$$

$$BaseLDH_i = \exp\left(TVBLDH + \eta_i^{BaseLDH}\right); TVBLDH = \begin{cases} Log\ BaseLDH & BECU = 0 \\ Log\ BaseLDH\ BECU & BECU = 1 \end{cases}$$

$$Emax_i = \frac{\exp\left(TVEmax + \eta_i^{Emax}\right)}{\exp\left(TVEmax + \eta_i^{Emax}\right) + 1}; TVEmax = \begin{cases} Logit\ Emax & BECU = 0 \\ Logit\ Emax\ BECU + ECU \cdot \theta_8 & BECU = 1 \end{cases}$$

$$EC50_i = \exp\left(TVEC50 + \eta_i^{EC50}\right)$$

where parameters are defined as follows:

- *LDHi* is the LDH level for the $i^{th}$ subject at a given pegcetacoplan concentration (C*i*).
- *BaseLDHi* is the baseline LDH level estimate for the $i^{th}$ subject, *TVBLDH* is log-transformed typical value of baseline LDH level in the population which takes the value of *Log BaseLDH* ($\theta_1$) for subjects receiving pegcetacoplan monotherapy at baseline (BECU=0) and the value of *Log BaseLDH BECU* ($\theta_2$) for subjects receiving eculizumab at baseline (BECU=1); ηiBaseLDH is the $i^{th}$ individual's deviation from the population baseline LDH on the log scale.
- *Emaxi* is the maximal proportional change from baseline in LDH level for the $i^{th}$ subject, *TVEmax* is the logit transformed typical value of Emax in the population which takes the value of logit Emax (θ3) when BECU=0, the value of logit Emax BECU (θ4) when BECU=1 and without time-varying eculizumab cotreatment (ECU=0), and the value of logit Emax BECU (θ4) plus θ8 when BECU=1 and ECU=1; *ηiEmax* is the $i^{th}$ individual's deviation from the population maximal effect on the logit scale.
- *EC50i* is the pegcetacoplan concentration at which 50% of the maximal effect is reached for the $i^{th}$ subject, *TVEC50* is the log-transformed typical value of EC50 in the population which takes the value of log EC50 (θ5); ηiEC50 is the $i^{th}$ individual's deviation from the population EC50 on the log scale.
- Hill (θ4) is the coefficient describing the sigmoidicity of the relationship between Hb level and pegcetacoplan concentration.

Source: APL-EX21-CP-011, Table 29.

Typical E-R parameters for the final updated LDH E-R model were stratified by baseline eculizumab treatment status. For eculizumab treatment–naive patients, the maximal effect of pegcetacoplan was estimated as a 91.7% decrease in LDH concentration from a baseline of 1920 IU/L. For eculizumab experienced patients, the maximal effect was estimated as a 20.0% decrease in LDH concentration from a baseline of 249 IU/L. A single EC50 of 187 µg/mL was estimated for both conditions with a common Hill coefficient estimated at 3.84, suggesting a steep pegcetacoplan concentration–LDH response relationship over the observed pegcetacoplan concentration range. Residual variability was estimated at 30.5%. Interindividual variability (CV) was 35.9% for EC50 and 44.7% for BaseLDH. Individual model-predicted values of BaseLDH and Emax were positively correlated (ρ = 0.719), such

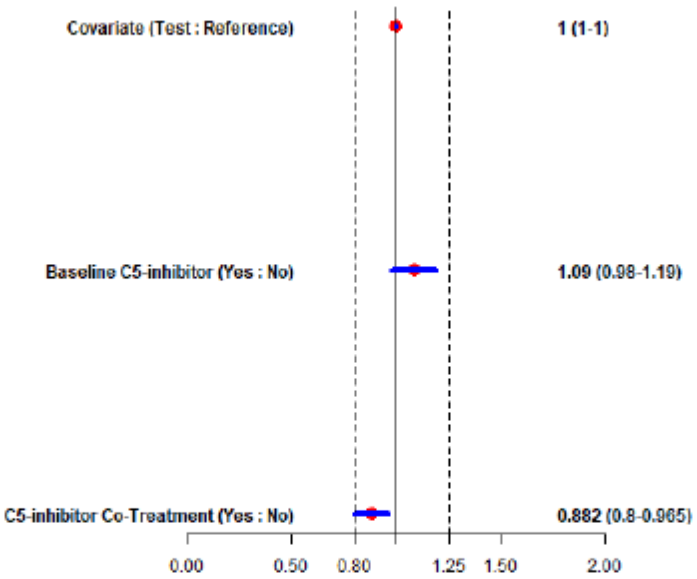
that individuals with higher baseline LDH had a greater proportional reduction with pegcetacoplan treatment. Similarly, Emax and EC50 were positively correlated (ρ = 0.556), such that individuals with greater maximal response also required higher pegcetacoplan concentrations to reach 50% of the maximal response.

Covariate Effects on LDH Response

Model-based simulations were performed to assess the impact of covariates on predicted LDH. Steady-state LDH levels were simulated for virtual subjects differing only in specific test conditions relative to reference conditions. The final updated model was selected for the simulations to illustrate impact (or lack thereof) of covariates that were retained in the final updated model. Test conditions were the alternative categories for categorical covariates.

Steady-state LDH concentration was determined as the average predicted LDH concentration over a one-week interval at steady state following dosing of pegcetacoplan 1080 mg SC twice weekly. Ratios (test:reference) and 90% CIs were calculated for each comparison and presented in a forest plot. Results are illustrated in Figure 25. Overall, the 90% CI for all covariates fell within the 0.8-1.25 reference range, indicating that none of these factors are anticipated to have meaningful effects on the steady-state LDH concentration achieved with pegcetacoplan treatment.

Other intrinsic patient factors of sex, Asian race, age, baseline C3 level, and baseline creatinine clearance are not predicted to have a meaningful impact on LDH response. No covariate effects, other than baseline eculizumab treatment status and time-varying eculizumab co-treatment, met criteria for retention in the final model, suggesting that LDH response is not influenced by other intrinsic or extrinsic patient factors.




Note: Red circles show the ratio of population-predicted LDH level under the test conditions compared to the reference at Week 16 following administration of the sorbitol formulation of pegcetacoplan 1080 mg subcutaneously twice weekly. The horizontal blue lines represent the corresponding 90% CI. Test conditions for categorical covariates were the alternative category. Vertical dashed lines indicate a reference interval of 0.8-1.25. Simulations (N = 1000) were performed for virtual subjects (one per test condition and reference), with parameter uncertainty incorporated using a smoothed parametric bootstrapping procedure based on the final updated model parameter estimates.
Source: Report APL-EX21-CP-011, Figure 24.

**Figure 6: Influence of covariates on predicted LDH level with 90% CI**

Applications of LDH Model

Simulations were performed using the PK and LDH E-R models to determine the predicted LDH response with pegcetacoplan 1080 mg SC twice weekly and every 3 days. In the simulation, complete covariate vectors were sampled with replacement for stationary covariates from adult patients with PNH in the modeling data set to generate 1000 virtual subjects. The median (5th, 95th) average pegcetacoplan concentration (Cavg,ss) was determined from 1000 simulated patients to provide reference exposure for assessment of LDH response under each dosing condition of interest.

The relationship between pegcetacoplan exposure at doses of 1080 mg SC twice weekly and every 3 days and maximum LDH response is described by the ratio of predicted Cavg,ss to different E-R model-predicted effect concentration thresholds and summarized in Table below. These results demonstrate that the median pegcetacoplan Cavg,ss exceeds the EC95 for LDH response with both dosing regimens and exceeds the EC99 at the increased dose of 1080 mg SC every 3 days.

**Table 18: Pegcetacoplan concentration and LDH response**

| Dosing regimen | Median $C_{avg,ss}$ (µg/mL) | Effect level | Pegcetacoplan concentration (µg/mL) | Ratio of median $C_{avg,ss}$ to concentration at the effect level |
|---|---|---|---|---|
| 1080 mg SC twice weekly | 667[a] | $EC_{50}$ | 187 | 3.56 |
| | | $EC_{80}$ | 280 | 2.38 |
| | | $EC_{90}$ | 356 | 1.87 |
| | | $EC_{95}$ | 442 | 1.51 |
| | | $EC_{99}$ | 717 | 0.930 |
| 1080 mg SC every 3 days | 766[a] | $EC_{50}$ | 187 | 4.09 |
| | | $EC_{80}$ | 280 | 2.73 |
| | | $EC_{90}$ | 356 | 2.15 |
| | | $EC_{95}$ | 442 | 1.73 |
| | | $EC_{99}$ | 717 | 1.07 |

Abbreviations: $C_{avg,ss}$ = average pegcetacoplan serum concentration at steady state; $EC_{nn}$ = concentration producing nn% of the maximal response; E-R = exposure-response; LDH = lactate dehydrogenase; PK = pharmacokinetic; SC = subcutaneous.

[a] Pegcetacoplan concentration and LDH level predictions were generated by sequential simulations based on the updated PK and LDH E-R models. Virtual subjects were generated by sampling 1000 covariate vectors with replacement from the observed data set. Individual PK parameter estimates were simulated using the updated PK model and appended to the simulation data set input into the LDH E-R model.

Source: Report APL-EX21-CP-011, Table 32.

The predicted pegcetacoplan Cavg,ss and LDH concentration are summarized below and stratified by baseline eculizumab treatment status. The median steady-state LDH in the simulation was less than the ULN from the reference laboratory regardless of prior eculizumab treatment status. Approximately 90.5% and 61.2% of simulated patients achieved steady-state LDH concentration <1.5× the ULN and LDH concentration less than the ULN, respectively, in the total population receiving 1080 mg SC twice weekly. Approximately 93.4% and 66% of simulated patients achieved steady-state LDH concentration <1.5× the ULN and LDH concentration less than the ULN, respectively, in the total population receiving 1080 mg SC every 3 days. A slightly greater proportion of patients with prior eculizumab treatment achieved LDH control below these thresholds than patients who were complement inhibitor–naive did.

**Table 19: Model-predicted pegcetacoplan concentration and LDH level**

| | Pegcetacoplan (µg/mL) | | LDH (IU/L) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient type | Dosing regimen | Median (90% PI) $C_{avg,ss}$ | 5th | 25th | 50th | 75th | 95th | Probability LDH <1.5× ULN[b] | Probability LDH <ULN[b] |
| All | 1080 mg SC twice weekly | 667[a] (423, 994) | 113 | 161 | 203 | 263 | 395 | 90.5% | 61.2% |
| Eculizumab-naive | | | 117 | 170 | 217 | 292 | 449 | 84.3% | 54.0% |
| Eculizumab-treated | | | 111 | 152 | 192 | 239 | 323 | 96.7% | 68.4% |
| All | 1080 mg SC every 3 days | 766[a] (508, 1128) | 106 | 152 | 193 | 248 | 364 | 93.4% | 66.0% |
| Eculizumab-naive | | | 105 | 148 | 192 | 260 | 426 | 90.3% | 64.1% |
| Eculizumab-treated | | | 107 | 155 | 196 | 242 | 325 | 96.5% | 68.0% |

Abbreviations: 90% PI = 90% prediction interval (5th to 95th percentiles); $C_{avg,ss}$ = average pegcetacoplan serum concentration at steady state; E-R = exposure-response; LDH = lactate dehydrogenase; PK = pharmacokinetic; SC = subcutaneous; ULN = upper limit of normal.

[a] Pegcetacoplan concentration and LDH level predictions were generated by sequential simulations based on the updated PK and LDH E-R models. Virtual subjects were generated by sampling 1000 covariate vectors with replacement from the observed data set. Individual PK parameter estimates were simulated using the updated PK model and appended to the simulation data set input into the LDH E-R model.

[b] ULN = 226 IU/L from the reference laboratory for Phase 3 studies.

Source: Report APL-EX21-CP-011, Table 33.

## 2.3.5. Discussion on clinical pharmacology

PD results were overall reassuring. The population PK model has been well updated to include results from study APL2-308 with patients with PNH not treated by C5 inhibitors, and the response effect models have also been well updated. An OC is raised on bioanalytics.

The pharmacokinetic (PK) results presented in the initial marketing authorization application included data from 4 studies in subjects with PNH: one pivotal Phase 3, controlled study (the 16-week randomized controlled period [RCP] of Study APL2-302 in complement inhibitor-experienced subjects with PNH) and 3 supportive studies. Of the supportive studies, 2 studies included subjects not being treated with eculizumab (Study APL2-CP-PNH-204 and Study APL2-202), and 1 study included subjects treated with eculizumab (Study APL-CP0514). Additionally, within variation application, clinical pharmacological studies were updated with results from the Study APL2-302 up to Week 48 and Study APL2-308.

Subsequently, the population PK model (APL-EX21-CP-010) and the population exposure-response (E-R, APL-EX21-CP-011) analysis was updated to include all available data from study APL2-302 (including the OLP up to Week 48) and study APL2-308.

Within this application, no new information has been provided with respect to characterization of PK in special populations or with regards to DDIs and none is required.

**Bioanalytical methods**

*Determination of pegcetacoplan concentrations*

Concentrations of pegcetacoplan were determined in serum using the liquid chromatography tandem mass spectrometry (LC-MS/MS) method.

The determination of pegcetacoplan in OLP of study 302 was performed at AIT Bioscience laboratory using the validated method which was assessed as adequate during initial MAA (BIO.VR.0210-1989).

The determination of pegcetacoplan in study APL2-308 was performed at Alturas Analytics laboratory using the newly developed HPLC/MS/MS method (AV20-APL2-02). Bioanalytical method developed at Alturas Analytics laboratory was satisfactorily validated with respect to precision, accuracy, sensitivity and selectivity, recovery, matrix effect, carryover and stability in accordance with the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1).

A cross-validation was performed involving four bioanalytical laboratories: AIT Bioscience, Agilex, Intertek and Alturas which showed comparability of results across different methods established at four different labs.

*Bioanalysis of study samples*

Spiked calibration standards and QC samples during analysis of study samples showed adequate precision and accuracy. Adequate number of samples was selected for ISR and ISR results met the acceptance criteria in all studies. All samples were analysed within the established long-term stability range for Study 302. For Study 308, most of the samples were analysed outside of the validated long term stability (up to 33 days at -70 °C days). The Applicant was asked to provide updated long term stability validation results for method AV20-APL2-02.

*ADA assays*

Anti-pegcetacoplan antibodies and neutralising antibodies were determined using the validated methods at BioAgilytix laboratory, assessed during the initial MAA. At that time, assay drug tolerance was assessed as low. According to the Applicant, development of assays to further improve drug tolerance is ongoing.

**Population PK model**

Existing popPK model was used to predict concentration-time profiles in the external data from PNH patients (studies 302 and 308) through external VPCs. While for study 302 VPCs showed good agreement between observed and simulated, for study 308 VPCs showed that central tendency of the pegcetacoplan concentration-time profile is slightly underpredicted. Therefore, applicant updated model to re-estimate the existing model parameters using the pooled analysis dataset. All parameters were estimated with good precision (RSE below 20%). Estimated parameters were very similar to the reference popPK model. VPCs for study 308 still showed underprediction in median, however the deviation in Study APL2-308 was further explored in a sensitivity analysis. Other diagnostic plots (PRED vs DV, WRES vs TIME and CONC) did not show any significant misspecification. Overall, popPK analysis seems acceptable.

The relationship between pegcetacoplan exposure and decrease in LDH concentration was adequately described using a sigmoidal Emax direct effect model. The maximal effect was a 91.7% decrease from a baseline of 1920 IU/L for complement inhibitor-naive patients. For patients switching from a C5 inhibitor to pegcetacoplan, the maximal effect was a 20.0% decrease from a baseline of 249 IU/L. The EC50 was estimated to be 187 µg/mL irrespective of complement inhibitor treatment history.

- The LDH E-R model supports the conclusion that the dosing regimen of 1080 mg twice weekly is effective for LDH response in both complement-naive patients and those switching from C5 inhibitor therapy. The median steady-state pegcetacoplan serum concentration of 667 µg/mL associated with this dosing regimen is expected to achieve at least 95% of the maximal predicted LDH reduction from baseline (Emax).

- Baseline eculizumab treatment status had an effect on baseline LDH and Emax. Median LDH at steady state following pegcetacoplan 1080 mg SC twice weekly is predicted to be 217 IU/L for complement inhibitor–naive patients and 192 IU/L for patients switching from eculizumab to pegcetacoplan treatment. Correspondingly, 84.3% and 96.7% of complement inhibitor–naive and eculizumab-to-pegcetacoplan switch patients are predicted to achieve LDH control below 1.5 times the ULN, respectively.
- Sex, Asian race, age, body weight, baseline creatinine clearance, and baseline C3 level are not anticipated to have meaningful effects on the LDH response to pegcetacoplan.

In the sensitivity analysis done to further evaluate the observed deviation of Study APL2-308, the estimate for the effect of Study APL2-308 on CL (-0.164) suggests that PNH patients from Study APL2-308 have approximately 16% lower clearance than PNH patients from other studies. Simulations have shown that the ratio of steady-state Cavg for Study APL2-308 relative to other PNH patient studies is predicted to be 1.20 (90% CI, 1.12-1.28), which indicates higher exposure for this study but with uncertainty (90% CI) overlapping with the reference interval of 0.8 to 1.25. This difference in exposure is unlikely to be clinically meaningful, however remains unexplained.

The effect of significant covariate body weight on pegcetacoplan exposure was further explored. For body weight range 53-93 kg ($5^{th}$ and $95^{th}$ percentiles of baseline body weights), the 90% CIs of test:reference ratio for Cavg,ss fell within or overlapped the 0.8-1.25 reference range. The reference was a PNH patient with body weight of 70 kg. Compared with a reference 70 kg patient, the steady-state average concentration is predicted to be approximately 20% higher in patients with a body weight of 50 kg. Patients weighing 40 kg are predicted to have a 45% higher average concentration. Minimal data are available on the safety profile of pegcetacoplan for patients with a body weight below 50 kg.

Therefore, effect of body weight on pegcetacoplan exposure is not found clinically significant. Further simulations on extreme body weights suggest 45% higher Cavg,ss in patients with body weight of 40 kg, while patients with body weight up to 160 kg are predicted to have around 41% lower exposure to pegcatacoplan.

Based on new data available and pop PK model parameter re-estimation, updates were implemented in the SmPC (see section 5.2.)

Updated data on absorption, body weight, bioavailability, volume of distribution and clearance is acceptable.

**Pharmacokinetics in target population**

Additional PK and PD data have become available from the open-label period (OLP) of study APL2-302 up to Week 48 and from Study APL2-308.

Sparse PK sampling was employed in studies APL2-302 and 308. Mean serum pegcetacoplan concentrations maintained at similar levels through 48 weeks in Study APL2-302, at 660 (194) µg/mL for pegcetacoplan group and 627 (178) µg/mL for eculizumab/pegcetacoplan group. In Study APL2-308, mean serum pegcetacoplan concentrations at Week 26 were somewhat higher, 767 (191) µg/mL for pegcetacoplan group and 820 (125) µg/mL for SoC to pegcetacoplan group. The reasons behind slightly higher exposure in Study APL2-308 were investigated using the updated Pop PK model.

**Immunogenicity**

Across studies APL2-302 and APL2-308, 3 out of 126 subjects who received pegcetacoplan were tested positive for anti-pegcetacoplan ADAs, and all were also tested positive for NAbs. ADAs did not have a noticable impact on the PK/PD, efficacy or safety of pegcetacoplan. The interpretation of this result

should be taken with care due to low drug tolerance of both assays employed. According to the Applicant, redevelopment and revalidation work is ongoing for both assays.

Very high proportion of subjects (105/126, 83%) tested positive for anti-PEG antibodies. Mostly, this was due to pre-existing anti-PEG antibodies in pre-dose samples. However, the incidence of treatment-emerging (9/126, 7.1%) and treatment-boosted (9/126, 7.1%) anti-PEG antibodies was low.

**Pharmacodynamics**

In Study APL2-302, data on complement biomarkers C3, CH50 and AH50 show sustained PD effects of pegcetacoplan through 48 weeks.

The mean percentage of PNH Type II + III RBCs was sustained from end of RCP through Week 48 and was close to 90%. The reduction in C3 deposition on Type II + III RBCs was maintained from the end of RCP to Week 48.

In Study APL2-308, AH50 values decreased rapidly following dosing with pegcetacoplan and the decrease was sustained through Week 26. CH50 values remained similar from baseline to Week 26. The mean C3 concentration increased from 0.95 g/L at baseline to 3.56 g/L at Week 26.

The mean percentage of PNH Type II + III RBCs increased to 90% at Week 26, suggestive of preventing hemolysis.

In pegcetacoplan group, a reduction in C3 deposition on Type II + III RBCs was observed at Week 4 and maintained through Week 26. Reduction in C3 deposition on Type II + III RBCs was also observed in the SoC to pegcetacoplan group, however less pronounced likely due to shorter duration of pegcetacoplan treatment in this group.

Overall, section 5.1 of the SmPC adequately describes PD effects of pegcetacoplan.

*Exposure-response model*

The exposure-response (E-R) model was updated with new available data on pegcetacoplan exposure and the clinical efficacy biomarkers of haemoglobin (Hb) and lactate dehydrogenase (LDH). E-R relationships between pegcetacoplan and Hb and LDH were both best described with sigmoidal direct Emax model as previously shown in initial MAA. However, the reference ER was used to describe Hb and LDH versus time and pegcetacoplan concentration for both Phase 3 studies (302 and 308).

While reference model adequately described Hb data for study 302, for study 308 reference model slightly underpredicts Hb over time in the pegcetacoplan cohort at later time points. Similar was shown for LDH data, where reference model showed for both 302 and 308 studies some underprediction of response.

Subsequently, both models were refined to improve predictive ability. In the final model for both PD markers, all parameters were estimated with good precision (RSE below 20%). Overall, the updated models seem to be generally consistent with previous results.

However, within this application, updated ER models are considered to have descriptive purpose and low regulatory impact.

## 2.3.6. Conclusions on clinical pharmacology

Results from the study patients not treated by C5 inhibitors are well reflected in the changes in section 5.2 of the SmPC, both for exposure, updated PK parameters, and effect of body weight on exposure. Plasma concentrations of pegcetacoplan in PNH patients not treated by C5 inhibitors (either naïve or having stopped C5 inhibitor therapy) can be considered both effective for improving Hb and control of

LDH levels.

## *2.4. Clinical efficacy*

No dose-response study nor supportive studies have been provided in this application.

### 2.4.1. Main study(ies)

**A Phase 3, randomized, multicenter, open-label, controlled study to evaluate the efficacy and safety of pegcetacoplan in patients with PNH (APL2-308)**

### *Methods*

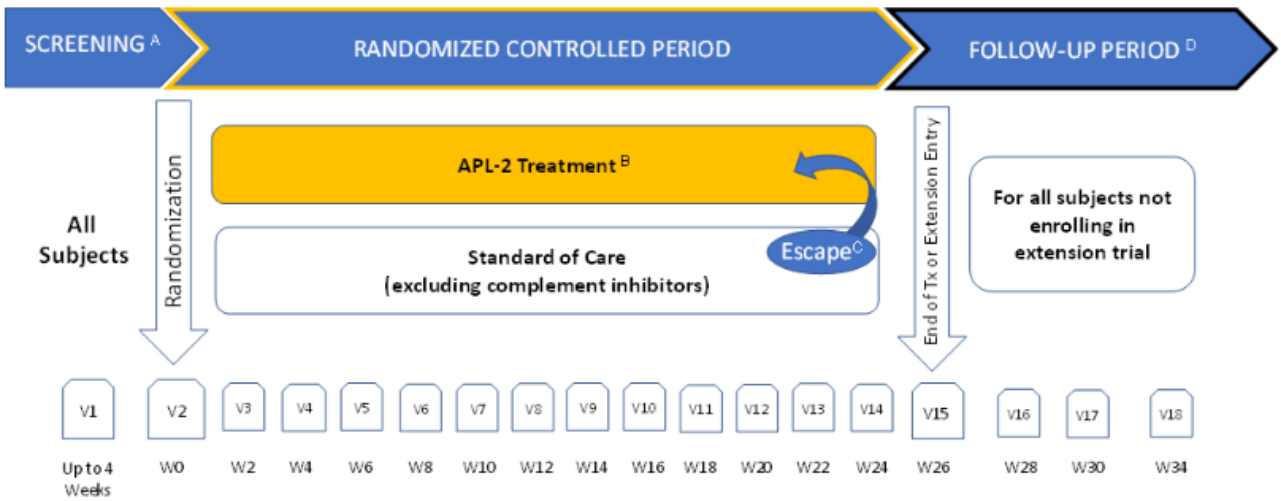



**Figure 7: Study APL2-308 design**

## Study participants

Inclusion criteria

For inclusion in the trial, each patient was required to fulfil all of the following criteria at the screening visit:

1. At least 18 years old (inclusive)
2. LDH concentration ≥1.5 × the upper limit of normal (ULN) at the screening visit
3. PNH diagnosis confirmed by high-sensitivity flow cytometry (granulocyte or monocyte clone >10%)
4. Hb concentration less than the lower limit of normal (LLN) at the screening visit
5. Ferritin concentration greater than or equal to the LLN or total iron binding capacity less than or equal to the ULN at the screening visit, according to central laboratory reference ranges. If a subject was receiving iron supplements at screening, the investigator must have ensured that the subject's dosage was stable for 4 weeks prior to screening, and it must have been maintained throughout the study. Subjects not receiving iron at screening must not have started iron supplementation during the course of the study.

6. Body mass index (BMI) ≤35 kg/m² at the screening visit
7. Platelet count of >50,000/mm$^3$ at the screening visit
8. Absolute neutrophil count (ANC) >500/mm$^3$ at the screening visit
9. Women of childbearing potential (WOCBP) must have had negative pregnancy tests at screening and must have agreed to use protocol-defined methods of contraception for the duration of the study and for 90 days after their last dose of study drug
10. Men must have agreed to use protocol-defined methods of contraception and to refrain from donating sperm for the duration of the study and for 90 days after their last dose of study drug

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the trial:

1. Treatment with any complement inhibitor (e.g., eculizumab) within 3 months prior to screening
2. Hereditary complement deficiency
3. History of bone marrow transplantation
4. Concomitant use of any of the following medications if the subject was not on a stable regimen for the specified time period prior to screening:
    - erythropoietin or immunosuppressants for at least 8 weeks
    - systemic corticosteroids for at least 4 weeks
    - vitamin K antagonists (e.g., warfarin) with a stable international normalized ratio for at least 4 weeks
    - iron supplements, vitamin B12, or folic acid for at least 4 weeks
    - low-molecular-weight heparin for at least 4 weeks
5. History or presence of hypersensitivity or idiosyncratic reaction to compounds related to the investigational product or SC administration
6. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days or 5 half-lives, whichever was longer
7. Planning to become pregnant or being a breastfeeding woman
8. History of meningococcal disease
9. Any comorbidity or condition (such as malignancy) that, in the opinion of the investigator, could have put the subject at increased risk or potentially confounded study data

## Treatments

Treatment administered

Starting at Visit 2 (Day 1), subjects assigned to the pegcetacoplan treatment arm received SC infusions of pegcetacoplan at a dosage of 1080 mg twice weekly. During the course of the study, subjects could have been switched to an alternative dosing regimen of pegcetacoplan at 1080 mg every 3 days, if warranted on the basis of clinical response and agreement from the sponsor.

Subjects were not to deviate from their pegcetacoplan dosing schedule: Day 1 and Day 4 of each treatment week (e.g., Monday/Thursday/Monday) or every 3 days (e.g., Monday/Thursday/Sunday).

*Pegcetacoplan dose adjustments*

Dosages above pegcetacoplan 1080 mg every third day were considered if they were clinically indicated. Prior to further dose escalation, the DMC and Independent Review Board (IRB)/IEC reviewed all cumulative safety, tolerability, and efficacy data (e.g., physical examination results, electrocardiogram (ECG) results, vital signs measurements, clinical laboratory test results, and AEs) and thoroughly assessed all safety data. PK/PD data and predicted exposure for subsequent doses based on emerging PK data was also reviewed prior to determining any proposed dose adjustment. No such dose adjustments were approved during the study.

Discontinuation with pegcetacoplan or noncompliance with the prescribed dose regimen might lead to the potential for an increased risk for serious haemolysis. Subjects should have been instructed to take their pegcetacoplan treatment as prescribed and to contact the investigator immediately for guidance in the event of any missed doses. If withdrawal of pegcetacoplan treatment was necessary or a subject completed the trial and did not elect to participate in the extension study, slow weaning was considered, and subjects should have been carefully monitored for at least 8 weeks to detect serious haemolysis or other complications, as detailed in the IB.

Prior and concomitant therapy

Prior medications (including vitamins and herbal preparations), including those discussed in the exclusion criteria, and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) the subject received or underwent within 28 days (or 2 years for documentation of vaccination) prior to the start of screening (Visit 1) until the first dose of study drug were recorded on the subject's case report form (CRF).

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information was recorded on the appropriate CRF page. Except for complement inhibitors (other than pegcetacoplan [e.g., eculizumab]) and/or phlebotomy/venesection for iron overload, any concomitant medication deemed necessary for the subject's SoC during the study or for the treatment of any AE (along with the allowed medications described below) was given at the discretion of the investigator.

The following concomitant medications were allowed if the specified conditions applied, and dose adjustments to the concomitant medication were not expected during the RCP (Visit 2 to Visit 15):

- erythropoietin, if the subject had been receiving a stable dosage for at least 8 weeks before screening
- immunosuppressants, if the subject had been receiving a stable dosage for at least 8 weeks before screening
- corticosteroids, if the subject had been receiving a stable dosage for at least 4 weeks before screening
- vitamin K antagonists (eg, warfarin) with a stable international normalized ratio for at least 4 weeks before screening
- iron supplements, vitamin B12, or folic acid, if the subject had been receiving a stable dosage for at least 4 weeks before screening. If subjects had previously received and tolerated iron chelation, this may have been continued or reinitiated throughout the study if clinically indicated and upon discussion with the sponsor's medical monitor.

- low-molecular-weight heparin, if the subject had been receiving a stable dosage for at least 4 weeks before screening

If clinically indicated and deemed in the best interest of the subject, the frequency or dose level of any of those concomitant medications could be adjusted by the investigator in consultation with the Apellis medical monitor.

Transfusion

During the study treatment period (Visit 2 [Week 0] to Visit 15 [Week 26]), transfusions were administered if subjects had either of the following:

- Hb concentration of <7 g/dL
- Hb concentration of <7 g/dL and <9 g/dL with symptoms

In addition, Hb concentration, LDH concentration, and reticulocyte count were assessed before any transfusion. The assessment was performed at a central or certified local laboratory.

If these criteria were not met and the principal investigator believed that a transfusion was necessary, the principal investigator discussed the situation with the sponsor before administering the transfusion. Transfusions that did not meet this criterion were considered protocol deviations and could lead to data being excluded from the per-protocol (PP) population.

Vaccination

To receive treatment with pegcetacoplan, subjects had to have documented evidence of vaccination against the following within 2 years of screening:

- *N. meningitidis* types A, C, W, Y, and B (administered as 2 separate vaccinations)
- *S. pneumoniae* (with a pneumococcal conjugate vaccine or pneumococcal polysaccharide vaccine 23 [PPSV23])
- H influenzae type B

**Subjects assigned to pegcetacoplan:** For subjects assigned to pegcetacoplan who did not have documented evidence of receiving any of the above vaccinations within 2 years prior to screening, the required missing vaccination(s) were administered at Visit 3 (Week 2) prior to dosing with pegcetacoplan (along with boosters administered during the study at or after Visit 7 [Week 10], if required [see below]). Vaccination was mandatory unless documented evidence existed that subjects were non-responders to vaccination (as evidenced by titers or display titer levels within acceptable local limits). The PI discussed individual subject circumstances with the sponsor.

If the subject required vaccination against *N. meningitidis*, a booster (for both vaccinations) was administered after at least 8 weeks (Visit 7).

If the subject required vaccination against *S. pneumoniae*, pneumococcal conjugate vaccine was administered at Visit 3, and PPSV23 was administered after at least 8 weeks (Visit 7) as a booster.

Subjects assigned to SoC (excluding complement inhibitors): Subjects who were initially assigned to SoC (excluding complement inhibitors) who became eligible for pegcetacoplan escape therapy received any required vaccination(s) 2 weeks after initiation of treatment with pegcetacoplan.

If required as detailed above, the *N. meningitidis booster* (for both vaccinations) and/or PPSV23 vaccination was administered at least 8 weeks following the initial vaccination(s).

Prophylactic Antibiotics

To receive treatment with pegcetacoplan, subjects required preventive antibiotics.

Subjects assigned to pegcetacoplan: Subjects were required to take ciprofloxacin 500 mg twice daily from Visit 2 (Week 0) to Visit 3 (Week 2) and continued to receive antibiotic prophylaxis until 14 days post vaccination. From that point forward, it was recommended that subjects take penicillin V 500 mg twice daily through the course of pegcetacoplan treatment.

Subjects assigned to SoC (excluding complement inhibitors): Subjects who were initially assigned to SoC (excluding complement inhibitors) did not need to initiate preventive antibiotic therapy at Day 1. If a subject became eligible for and initiated pegcetacoplan escape therapy, the subject was required to take ciprofloxacin 500 mg twice daily for 2 weeks, beginning on the first day of treatment with pegcetacoplan and continued to receive antibiotic prophylaxis until 14 days post vaccination. After 2 weeks of ciprofloxacin, it was recommended that subjects take penicillin V 500 mg twice daily through the course of pegcetacoplan treatment.

Rescue Antibiotics

Body temperature, vital signs measurements, and relevant blood parameters were monitored regularly throughout the study to assess for signs of infection. Subjects were provided with emergency study cards that included a list of symptoms associated with infections. This study card also guided subjects with instructions to contact their study physician or seek emergency medical care in the event they had any of the listed symptoms. In the event of a suspected infection, the principal investigator provided guidance on appropriate action to be taken thereafter. Action taken may have included administration of a broad-spectrum antibiotic.

## Objectives

## Outcomes/endpoints

Primary efficacy endpoints

The primary objective of this study was to evaluate the efficacy of pegcetacoplan, compared to SoC (excluding complement inhibitors), in subjects with PNH, as assessed by:

- Hb stabilization, defined as avoidance of a >1 g/dL decrease in Hb concentration from baseline in the absence of transfusion through Week 26 (yes/no)

AND

- reduction in LDH concentration from baseline to Week 26

Key secondary efficacy endpoints

1. Hb response (yes/no) in the absence of transfusions (Hb response was defined as a ≥1 g/dL increase in Hb from baseline at Week 26)
2. Change from baseline to Week 26 in ARC

3. Change from baseline through Week 26 in Hb concentration
4. Proportion of subjects who received transfusion or had decrease of Hb >2 g/dL from baseline (yes/no)
5. Transfusion avoidance (yes/no), defined as the proportion of subjects who did not require a transfusion during the RCP. Note that the initial definition of transfusion avoidance was modified to be consistent with the definition used in the other Phase 3 study of PNH.
6. Number of packed red blood cell (PRBC) units transfused from baseline to Week 26
7. Change from baseline to Week 26 in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale score
8. Normalization of Hb concentrations (defined as ≥1× the lower limit of normal [LLN]) from baseline through Week 26 in the absence of transfusions (yes/no)
9. Normalization of LDH concentrations of ≤1× the upper limit of normal (ULN) from Week 4 through Week 26 in the absence of transfusions (yes/no)
10. Change from baseline to Week 26 in European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (Version 3) scores
11. Change from baseline through Week 26 in Linear Analog Scale Assessment (LASA) scores (Version 3)
12. ARC normalization (<1× the ULN) at Week 26 (yes/no)
13. Time to failure of Hb stabilization
14. Time to first transfusion

Additional secondary efficacy endpoints

The following additional secondary endpoints are summarized by treatment group using the intent-to-treat (ITT) set:

15. Number and percentage of subjects who achieved Hb concentrations ≥11 g/dL and ≥12 g/dL at Week 26
16. Number and percentage of subjects without PRBC transfusion during the RCP
17. Total and indirect bilirubin normalization (defined as ≤1× the ULN) at Week 26 in the absence of transfusion (yes/no)
18. Number and percentage of subjects achieving ≥3 points of improvement in FACIT-Fatigue Scale score from baseline through Week 26
19. Normalization of Hb concentrations (defined as ≥1× the LLN) from baseline at Week 26 in the absence of transfusions (yes/no)
20. Normalization of LDH concentrations ≤1× the ULN at Week 26 in the absence of transfusions (yes/no)
21. ARC normalization (<1× the ULN) from baseline through Week 26 in the absence of transfusion (yes/no)

22. Normalization of LDH concentrations (yes/no) of ≤1× the ULN from baseline through Week 26 in the absence of transfusions (yes/no)
23. Normalization of Hb concentrations (defined as ≥1× the LLN) from Week 4 through Week 26 in the absence of transfusions (yes/no)
24. ARC normalization (<1× the ULN) from Week 4 through Week 26 in the absence of transfusion (yes/no)

Exploratory endpoints

- The proportion of patients with breakthrough haemolysis as assessed by at least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue; haemoglobinuria; abdominal pain; shortness of breath [dyspnoea]; anaemia [Hb concentration <10 g/dL]; major adverse vascular events, including thrombosis; dysphagia; or erectile dysfunction) in the presence of elevated LDH concentration ≥2× the ULN, after prior LDH concentration reduction to <1.5× the ULN on therapy

## Sample size

Forty-eight subjects assigned to treatment (32 subjects to pegcetacoplan and 16 subjects to SoC) were required for the study to achieve 90% power at the 5% significance level (2-sided) using a 2-group Fisher exact test with unequal allocation 2:1 to treatment groups (pegcetacoplan and SoC) to detect the effect of pegcetacoplan on Hb stabilization compared with that of the SoC, assuming an increase of 45% in the proportion of subjects achieving Hb stabilization with pegcetacoplan over SoC (ie, a change from 5% [no treatment] to 50% [pegcetacoplan]). With the same number of subjects and assuming an effect size of at least 1.2, the study was at 96% power for the LDH reduction endpoint.

To account for loss of power due to discontinuations, the study attempted to assign approximately 54 subjects to treatment.

## Randomisation

The randomization was performed on a 2-to-1 ratio basis. It was stratified by the number of PRBCs transfused within the 12 months prior to screening (<4; ≥4) (i.e., number of transfusion events regardless of PRBC units transfused).

## Blinding (masking)

There was no blinding of treatments assigned to patients.

## Statistical methods

### Analysis sets

*Screened Set*

The screened set included all subjects who signed the ICF. This set was used only for the purpose of describing subject disposition.

Safety Set

The safety included all subjects who received at least 1 dose of study medication (pegcetacoplan) and all subjects who were randomized to SoC (excluding complement inhibitors). Subjects were analyzed according to the treatment they received. Subjects who escaped to pegcetacoplan were included in the pegcetacoplan treatment group from the time of first dose with pegcetacoplan and onward.

ITT Set

The ITT set included all subjects assigned to treatment. Subjects were analyzed according to their assigned treatment, regardless of the treatment actually received. The handling of data for subjects who escaped to pegcetacoplan treatment are discussed, as relevant, in the sections below.

PP Set

The PP set included all subjects in the ITT set who had not violated any inclusion or exclusion criteria or deviated from the protocol in a way that could influence their efficacy assessment. Decisions concerning the exclusion of subjects from the PP analysis set were made and documented prior to database lock.

**Efficacy Analyses**

The efficacy endpoints were primarily evaluated with the ITT set. All statistical testing was at the 5% level of significance (2-sided), and all point estimates for the comparison between treatment groups were accompanied by 2-sided 95% CIs. All possible efforts were made to ensure that subjects completed all the required assessments. Because missing data could have potentially biased the outcome of the statistical analyses and the subsequent estimation of the magnitude of the treatment effect, different strategies were applied to provide a balanced assessment of treatment efficacy. Endpoints were summarized and, where appropriate, plotted over time for each treatment group.

**Table 20: Summary of Estimands**

| | | | | |
|---|---|---|---|---|
| (LDH) level from Baseline to Week 26 | ITT | Week 26 LDH level change from baseline | Any LDH values before escape from SOC to pegcetacoplan will be used in the analysis and all values after the SOC escape will be set to missing. | Difference between treatment means with 95% confidence interval and appropriate p-value based on ANCOVA adjusting for LDH baseline, treatment, and stratification factor. |
| | **Sensitivity Analyses** | | | |
| | ITT | Week 26 LDH level change from baseline | The strategy will be the same as for the second co-primary endpoint shown above. | Difference between treatment means with 95% confidence interval and appropriate p-value based on Mixed Model for Repeated Measures (MMRM) |
| | | | | |
| | ITT | Week 26 LDH level change from baseline | Imputation based on the delta-adjusted stress testing method (Tipping Point) using the strategy will be the same as for the second co-primary endpoint shown above. | Difference between treatment means with 95% confidence interval and appropriate p-value based on MMRM |
| | **Supportive Analyses** | | | |
| | ITT | Week 26 LDH level change from baseline | The strategy will be the same as for the second co-primary endpoint with Last observation carried forward (LOCF) approach for handling missing data using the strategy will be the same as for the second co-primary endpoint shown above. | Difference between treatment means with 95% confidence interval and appropriate p-value based on ANCOVA adjusting for LDH baseline, treatment, and stratification factor. |
| | ITT | Week 26 LDH level change from baseline | The strategy will be the same as for the second co-primary endpoint with Best observation carried forward (BOCF) approach for handling missing data. | Difference between treatment means with 95% confidence interval and appropriate p-value based on ANCOVA adjusting for LDH baseline, treatment, and stratification factor. |
| | PP | Week 26 Hb change from baseline | The strategy will be the same as for the second co-primary endpoint. | Difference between treatment means with 95% confidence interval and appropriate p-value based on ANCOVA adjusting for LDH baseline, treatment, and stratification factor. |
| | | | | |
| | | | | |

Baseline was taken at Day 1 as the average of measurements prior to the first dose of pegcetacoplan or prior to randomization to the SoC treatment group for efficacy endpoints.

To preserve the Type 1 error, a fixed-sequence testing strategy was used; hence, statistical significance with the first secondary endpoint (Week 26 Hb response in the absence of transfusion [yes/no]) was concluded only if statistical significance was achieved with the primary analysis of the coprimary endpoints.

The ordering of the secondary endpoints in this testing strategy matched the order in which they are presented in the secondary efficacy endpoints.

For the first coprimary endpoint, the numbers and percentages of subjects who achieved Hb stabilization for the 2 treatment groups were computed and compared using a stratified Cochran-Mantel-Haenszel (CMH) chi-square test. The adjusted odds ratio of achieving Hb stabilization for the

pegcetacoplan group vs the SoC group and the associated 95% CI are presented along with the difference between treatment groups in percentages of subjects who achieved Hb stabilization with associated 95% CI.

Subjects who received a transfusion through Week 26, escaped from the SoC treatment group to the pegcetacoplan treatment group, withdrew from the study and treatment, or were lost to follow-up before providing primary efficacy assessment were categorized as not achieving Hb stabilization.

The second coprimary efficacy endpoint is the change from baseline in LDH concentration at Week 26. If a subject escaped from the SoC treatment group to the pegcetacoplan treatment group, the LDH concentration up to escape was included in the model. If a subject received a transfusion, the pretransfusion LDH concentration from the certified local laboratory was used; however, if the concentration was not assessed or was missing, the pretransfusion central laboratory LDH value was used.

The missing data was handled using a multiple imputation method based on the assumption of missing at random (MAR). Because missing data could bias the outcome of the statistical analyses and the subsequent estimation of the magnitude of the treatment effect, the following sensitivity and supportive analyses were performed to evaluate the robustness of the results from the primary analysis methods.

**Sensitivity Analyses**

No sensitivity analysis was performed for the first coprimary analysis, and this section presents only the sensitivity analyses for the second coprimary endpoint.

A mixed-effects model for repeated measures (MMRM) was used as the first sensitivity analysis for the second coprimary endpoint (change in LDH concentration from baseline at Week 26) after setting values to missing when subjects escape from the SoC to pegcetacoplan.

The between-treatment-group comparison for the second coprimary efficacy endpoint was performed using an MMRM (Mallinckrodt et al. 2008). The model included fixed categorical effects for treatment group, study visit, stratification variable (based on transfusion history), and the visit-by–treatment group interaction, as well as the continuous, fixed covariate of baseline LDH concentration. Initially an unstructured covariance matrix was investigated. If this analysis failed to converge, other structures, such as compound symmetry, were tested.

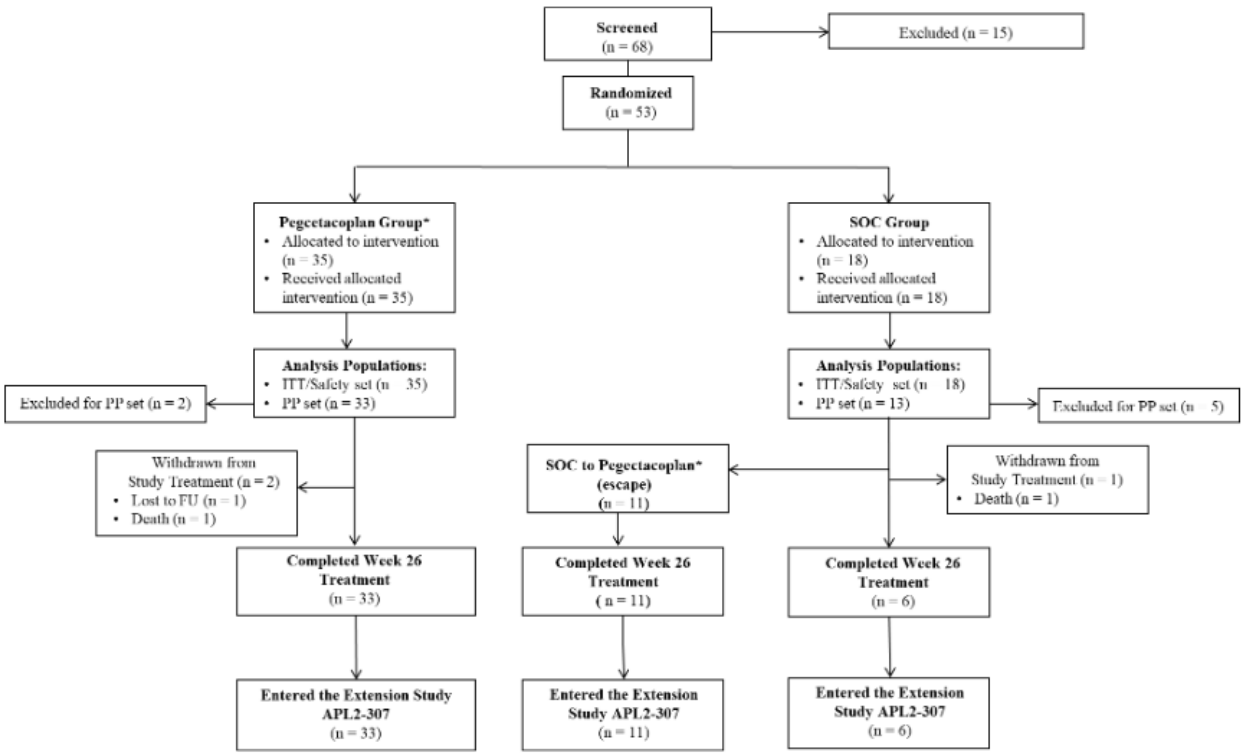
The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The difference between pegcetacoplan and SoC mean LDH concentration changes from baseline at Week 26 were calculated along with its 2-sided 95% CI and associated *P* value from the MMRM model.

In addition, the imputation based on the delta-adjusted stress testing (tipping point) analysis was performed for the second coprimary endpoint (mean LDH concentration change from baseline at Week 26) using an MMRM model. This method can be considered a sensitivity analysis for the second coprimary MAR-based analyses where deterioration of the future unobserved outcomes constitutes specific types of departure from the MAR assumption toward the missingness not at random assumption.

The tipping point imputation approach will be based on the delta-adjusted stress testing method (O'Kelly and Ratitch 2014). This method assumes that subjects who discontinue from the pegcetacoplan group experience worsening, defined by a prespecified adjustment in the second coprimary endpoint (LDH concentration). After the initial imputation, a range of shifts were added to the imputed missing data in the pegcetacoplan group.

## *Results*

## Participant flow




Abbreviations: FU = follow-up; ITT = intent-to-treat; n = number of subjects; PP = per-protocol; SOC = standard of care; SoC = standard of care.
*A total of 46 subjects (35 in the pegcetacoplan group and 11 in the SoC to pegcetacoplan [escape]) group received at least 1 dose of pegcetacoplan.
Sources: Table 14.1.1.1; Table 14.1.2.1; Table 14.1.2.2.

**Figure 8: APL2-308 Participant flow**

Sixty-eight subjects were screened, and 15 subjects (22.1%) failed screening. The reasons for screen failure among the 15 subjects included comorbidities, inadequate vaccination, and inadequate levels of LDH, Hb, ferritin (or total iron binding capacity), platelets, or neutrophils. Nine subjects had multiple reasons for screen failure.

Fifty-three subjects entered the RCP: 35 in the pegcetacoplan group and 18 in the SoC group. Eleven subjects in the SoC group escaped to the pegcetacoplan group. Overall, 46 subjects received at least 1 dose of pegcetacoplan.

All 50 subjects who completed the RCP opted to enter the extension study (Study APL2-307). Twelve of these 50 subjects remained on study past Week 48 awaiting rollover to the extension study. Only the 3 subjects who withdrew from study treatment did not enter the extension study.

## Numbers analysed

The table below shows the analysis population.

**Table 21: Analysis populations**

| Analysis population | Pegcetacoplan | SoC | Total |
|---|---|---|---|
| Screened set, n | – | – | 68 |
| Intent-to-treat set,[a] n | 35 | 18 | 53 |
| Safety set,[b] n (%) | 35 (100) | 18 (100) | 53 (100) |
| Per-protocol set,[c] n (%) | 33 (94.3) | 13 (72.2) | 46 (86.8) |
| Pharmacokinetic set,[d] n (%) | 34 (97.1) | – | 45 (84.9)e |
| Pharmacodynamic set,[f] n (%) | 34 (97.1) | 18 (100) | 52 (98.1) |

Abbreviations: n = number of subjects; SoC = standard of care.
Notes: Percentage is based on the number of subjects in the intent-to-treat set.
[a] The intent-to-treat set includes all randomized subjects. Subjects were analyzed according to their assigned treatment, regardless of the treatment they received.
[b] The safety set includes all subjects who received at least 1 dose of study medication (pegcetacoplan) and subjects who were randomized to SoC. Subjects were analyzed according to the treatment they received.
[c] The per-protocol set includes all subjects in the ITT set who did not have any major protocol deviation that could potentially impact final data analyses. The analyses using this set were based upon the randomized treatment group allocated.
[d] The PK set includes all subjects in the ITT analysis set who had at least 1 evaluable (ie, not impacted by any important protocol deviations or other events) postdose PK measurement (even if it was below the limit of quantification). The analyses using this set were based upon the actual treatment received.
• 11 subjects who escaped from the SoC group to pegcetacoplan group are included.
[f] The PD set includes all subjects in the ITT analysis set who had at least 1 evaluable (ie, not impacted by any important protocol deviations or other events) postdose PD measurement (even if it was below the limit of quantification). The analyses using this set were based upon the actual treatment received.
Source: Table 14.1.1.1.

The ITT and safety sets are identical, and all subjects received the treatment they were assigned. Two subjects from the pegcetacoplan group and 5 subjects from the SoC group were excluded from the PP set because of protocol deviations, including deviations due to investigational product dosing, AE reporting, and missing tests.

One patient is missing from both the PK and PD sets because a post-baseline blood draw was not done.

## Recruitment

Twenty-two sites participated in this study across Hong Kong, Malaysia, Philippines, Singapore, Thailand, Columbia, Mexico, and Peru.

- Data first patient enrolled: 27 August 2019
- Data last patient completed: 23 June 2021
- Release date of the clinical study report (CSR): 27 October 2021

## Conduct of the study

Protocol amendments

The table provides a summary and brief description of the changes made in the Study APL2-308 protocol.

**Table 22: Summary and brief description of the changes made in the Study APL2-308 protocol**

| Protocol Amendment effective date | Main changes made |
|---|---|
| Protocol Amendment 1<br>05 March 2019 | • Updates throughout to mandate prophylactic antibiotic therapy for 14 days post vaccination<br>• Definitions of co-primary objectives/endpoints were clarified<br>• Secondary objectives were re-ordered<br>• The following secondary objective was added: Normalization of Hb levels (defined as ≥1x ULN) from baseline at Week 26 in the absence of transfusions (Yes/No)<br>• The following safety objective was added to correct an error of omission: Incidence of anti-APL2 antibodies<br>• To ensure equal distribution of baseline characteristics across treatment groups, stratification at randomization was clarified: Randomization will be stratified by the following values: number of PRBC transfusions within the 12 months prior to screening (≤4; >4) (i.e., number of transfusion events regardless of PRBC units transfused) ~~Number of PRBCs transfused within the 12 months prior to screening (≤3; >3)~~<br>~~LDH at screening (<3 x ULN; ithin the~~<br>• The following inclusion criterion was modified to exclude subjects with Class 2 or greater obesity from enrolling in the study (subjects with a BMI ≥35.0 kg/m², as defined by the US CDC's criteria [CDC 2016]).<br>• The criteria for escape therapy was clarified as follows: Following Visit 2 (Week 0), subjects assigned to the SoC (excluding complement inhibitors) treatment arm who have an Hb level measured by the central laboratory that is **≥2 g/dL** below the baseline value will be offered the opportunity to receive escape therapy with APL-2. ~~(i.e., subjects who fail the first coprimary endpoint will commence APL-2 escape therapy).~~<br>• PK assessment was changed to Weeks 0, 4, 8, 12, 20, 26, and 30.<br>• Complement profile assessment (CH50, AH50) was changed to Weeks 0, 4, 8, 12, 20, 26, and 30.<br>• C3 assessment was separated out from complement profile and changed to every clinic visit except Screening and APL-2 Initiation Visit (AIV). |
| Protocol Amendment 2<br>20 May 2020 | • Added COVID-19 pandemic-related information<br>• PK sample collection and complement profile sample collection timepoints shown on the schedule of events (SOE) were updated to accurately reflect changes made in Amendment 1. The Week 2 draw was removed and a Week 8 draw was added for both PK and complement sample collection.<br>• Added benefit/risk information regarding pegcetacoplan use and the potential risks/complications with COVID-19 |

| | |
|---|---|
| | • Deleted the following as a secondary objective: Change from Baseline to Week 26 in Hb level<br>• Added information related to an altitude correction factor for Hb in subjects living at altitudes ≥1000 meters above sea level<br>• A typo in the PRBC transfusion stratification categories (was changed from (≤4; >4) to (<4, ≥4)) was corrected.<br>• The statement regarding scheduling of DMC meetings was removed to allow scheduling flexibility<br>• The LDH criterion for dose increase was changed in order to allow consideration of more frequent dosing to occur after 1 instance of an LDH result of ≥2 x ULN, instead of 2 consecutive occasions at least one week apart<br>• It was clarified that SAEs not considered related to study drug, or in patients randomized to the standard of care, do not have to be reported to regulatory authorities |
| Protocol Amendment 3<br>10 August 2020 | • Removed language regarding an altitude correction factor for Hb because no subjects enrolled in the study live at altitudes ≥nrolled in the study live at Added a section regarding the collection of COVID-19 test results.<br>• Added a new section, Section 9.5.1.24, regarding drug abuse, misuse, overdose, and medication error. |

*Changes to the initial SAP*

The following relevant changes from the initial SAP have been introduced in the final SAP (Version 3; CSR, Appendix 16.1.9) before database lock:

- The second co-primary analysis specified in the protocol has been replaced by an ANCOVA analysis. The analysis specified in the protocol (MMRM) was performed as a sensitivity analysis.
- Two sensitivity analyses for the second co-primary endpoints (change from baseline to Week 26 for LDH) were added: MMRM and tipping point analysis based on the delta-adjusted stress testing method. These analyses were not specified in the protocol.
- Additional secondary endpoints were added:
    - proportion of subjects who received transfusion or had decrease of Hb concentration >2 g/dL from baseline (yes/no)
    - transfusion avoidance (yes/no), defined as the proportion of subjects who did not require a transfusion during the RCP

The following modifications were made between the final SAP and the analyses presented in the clinical study report (CSR):

- The transfusion avoidance endpoint in the SAP (fifth secondary endpoint) was not clearly defined and led to the following modification in the analyses:
    - In this study report, transfusion avoidance is defined as follows: the proportion of subjects who did not require a transfusion during the RCP. Subjects who did not have a

transfusion but withdrew before Week 26 or escaped from SoC to pegcetacoplan were not considered to have achieved transfusion avoidance.

- The initial definition of transfusion avoidance included in the SAP (ie, the proportion of subjects who did not require a transfusion during the RCP) was maintained; the analysis is reclassified and presented in the study report as transfusion free.

During the normalization process of the laboratory parameters using the location-scale normalization formula as described in Version 3 of the SAP, certain normalized laboratory values (ie, platelet counts) for 2 subjects (Subjects 40140005 and 40141002) resulted in negative values; these negative values were expected because of the very low platelet counts reported. To avoid this situation the lower scale formula [central value = local value × NRLO (central laboratory) / NRLO (local laboratory)] was used which resulted in meaningful normalized values. Normalization of Hb, ARC, and LDH are specified 3 ways in the SAP:

1. Normalization at Week 26
2. Normalization from baseline to Week 26
3. Normalization from Week 4 to Week 26

In this document, the normalizations at Week 26 are the primary assessments because normalization at a given time point is more clinically meaningful than normalization over a period of time.

An ad hoc analysis of the number and percentage of subjects achieving Hb stabilization from baseline through Week 26 in the absence of transfusion, where Hb stabilization is defined as avoidance of a >2 g/dL decrease in Hb concentration from baseline, is included in the CSR, (not shown here).

Protocol deviations

A major protocol deviation was defined as noncompliance with the approved study protocol, whether intentional or unintentional, that could significantly adversely affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the data. Subjects with major protocol deviations that could impact data interpretation were excluded from the PP data set. The table below summarizes protocol deviations and major protocol deviations.

**Table 23: Summary of Protocol Deviations and Major Protocol Deviations by Study**

| | Pegcetacoplan (N = 35) | SoC (N = 18) | Total (N = 53) |
|---|---|---|---|
| Any protocol deviation, n (%) | 32 (91.4) | 17 (94.4) | 49 (92.5) |
| Documentation/AE reporting, n (%) | 4 (11.4) | 3 (16.7) | 7 (13.2) |
| IP dosing, n (%) | 8 (22.9) | 1 (5.6) | 9 (17.0) |
| Prohibited concomitant medication, n (%) | 1 (2.9) | 0 | 1 (1.9) |
| Tests/assessments/procedures, n (%) | 30 (85.7) | 14 (77.8) | 44 (83.0) |
| Other, n (%) | 17 (48.6) | 2 (11.1) | 19 (35.8) |
| Any major protocol deviation, n (%) | 13 (37.1) | 6 (33.3) | 19 (35.8) |
| Documentation/AE reporting, n (%) | 2 (5.7) | 1 (5.6) | 3 (5.7) |
| IP dosing, n (%) | 4 (11.4) | 1 (5.6) | 5 (9.4) |
| Prohibited concomitant medication, n (%) | 1 (2.9) | 0 | 1 (1.9) |
| Tests/assessments/procedures, n (%) | 9 (25.7) | 4 (22.2) | 13 (24.5) |
| Other, n (%) | 2 (5.7) | 1 (5.6) | 3 (5.7) |

Abbreviations: AE = adverse event; IP = investigational product; ITT = intent-to-treat; N = number of subjects in treatment group; n = number of subjects in parameter; SoC = standard of care.
Notes: Data collected after escape from SoC to pegcetacoplan are excluded.
Source: Table 14.1.3.1.1 and Table 14.1.3.2.1.1.

In the study, 19 subjects (35.8%) had protocol deviations that were determined to be major deviations, as defined in the previous paragraph. A similar percentage of these were from each treatment group: 37.1% in the pegcetacoplan group and 33.3% in the SoC group.

Most major protocol deviations (13 subjects; 24.5%) involved study assessments and procedures: 9 subjects (25.7%) in the pegcetacoplan group and 4 subjects (22.2%) in the SoC group. Reasons for these deviations included missed visits due to hospitalizations or loss of follow-up, missed transfusions due to investigator decisions, lack of a local laboratory due to COVID-19, and assessments and vaccinations not completed as per protocol.

Five subjects (9.4%) had major protocol deviations related to study drug noncompliance (4 subjects in the pegcetacoplan group and 1 subject who escaped the SoC group). Three subjects (5.7%) had major protocol deviations related to documentation and AE reporting, and the 3 major protocol deviations classified as "other" were all due to COVID-19 constraints.

One subject (1.9%) had a major protocol deviation related to prohibited concomitant medication when folic acid for SoC treatment was initiated in a subject in the pegcetacoplan group without consultation with the sponsor's medical monitor.

COVID-19 impacted some of these major protocol deviations. Six subjects had major protocol deviations because of constraints associated with COVID-19, such as travel restrictions precluding the use of the central laboratory, quarantine, and paperwork delays preventing study rollover and laboratory work from a local laboratory. The major protocol deviations related to COVID-19 were in the tests/assessments/procedures category and "other" category and were among 5 subjects in the pegcetacoplan group and 1 subject in the SoC group.

## Baseline data

Demographics

Demographic characteristics by treatment group for the ITT set are presented in the table below.

**Table 24: Demographic Characteristics by Treatment Group (ITT Set)**

| | **Pegcetacoplan (N = 35)** | **SoC (N = 18)** | **Total (N = 53)** |
|---|---|---|---|
| Age, years | | | |
| Mean (SD) | 42.2 (12.70) | 49.1 (15.64) | 44.5 (14.00) |
| Min, max | 22, 67 | 20, 74 | 20, 74 |
| <65, n (%) | 33 (94.3) | 14 (77.8) | 47 (88.7) |
| ≥65 and <75,[a] n (%) | 2 (5.7) | 4 (22.2) | 6 (11.3) |
| Sex | | | |
| Female, n (%) | 16 (45.7) | 8 (44.4) | 24 (45.3) |
| Male, n (%) | 19 (54.3) | 10 (55.6) | 29 (54.7) |
| Race[b] | | | |
| Black or African American, n (%) | 2 (5.7) | 0 | 2 (3.8) |
| American Indian or Alaska Native, n (%) | 9 (25.7) | 2 (11.1) | 11 (20.8) |
| Asian, n (%) | 23 (65.7) | 16 (88.9) | 39 (73.6) |
| Other, n (%) | 1 (2.9) | 0 | 1 (1.9) |
| Ethnicity | | | |
| Hispanic or Latino, n (%) | 12 (34.3) | 2 (11.1) | 14 (26.4) |
| Not Hispanic or Latino, n (%) | 23 (65.7) | 16 (88.9) | 39 (73.6) |
| Region | | | |
| Latin America, n (%) | 12 (34.3) | 2 (11.1) | 14 (26.4) |
| Asia Pacific, n (%) | 23 (65.7) | 16 (88.9) | 39 (73.6) |
| Weight (kg) | | | |
| Mean (SD) | 65.08 (13.279) | 61.08 (9.923) | 63.72 (12.293) |
| Min, max | 41.0, 95.0 | 43.9, 77.3 | 41.0, 95.0 |

| | | | |
|---|---|---|---|
| Height (cm) | | | |
| Mean (SD) | 164.52 (7.627) | 162.44 (7.725) | 163.82 (7.650) |
| BMI ($kg/m^2$) | | | |
| Mean (SD) | 24.00 (4.428) | 23.07 (2.939) | 23.68 (3.980) |
| Min, max | 17.2, 34.4 | 19.0, 30.3 | 17.2, 34.4 |
| <18.5, n (%) | 3 (8.6) | 0 | 3 (5.7) |
| ≥18.5-<25, n (%) | 22 (62.9) | 13 (72.2) | 35 (66.0) |
| ≥25-<30, n (%) | 6 (17.1) | 4 (22.2) | 10 (18.9) |
| ≥30-<35, n (%) | 4 (11.4) | 1 (5.6) | 5 (9.4) |
| ≥35, n (%) | 0 | 0 | 0 |

Abbreviations: BMI = body mass index; ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects in treatment group; n = number of subjects in parameter; SoC = standard of care.
[a] No subjects in the study were ≥75 years in age.
[b] No subject in the study was White, native Hawaiian, or other Pacific Islander.
Source: Table 14.1.4.1.1.

Disease characteristics

**Table 25: Baseline Characteristics by Treatment Group (ITT Set)**

| Characteristics | Statistics | Pegcetacoplan (N = 35) | SoC (N = 18) | Total (N = 53) |
|---|---|---|---|---|
| Time since diagnosis of PNH (years) to Visit 2 (Week 0) | n | 35 | 18 | 53 |
| | Mean (SD) | 5.663 (5.9189) | 5.490 (5.1453) | 5.604 (5.6186) |
| Number of PRBC transfusions in the last 12 months prior to screening[a] | n | 35 | 18 | 53 |
| | Mean (SD) | 3.9 (4.37) | 5.1 (4.98) | 4.3 (4.57) |
| <4[b] | n (%) | 21 (60.0) | 8 (44.4) | 29 (54.7) |
| ≥4[b] | n (%) | 14 (40.0) | 10 (55.6) | 24 (45.3) |
| Number of subjects who never received PRBC transfusion | n (%) | 6 (17.1) | 4 (22.2) | 10 (18.9) |
| Number of subjects who received at least one PRBC transfusion | n (%) | 29 (82.9) | 14 (77.8) | 43 (81.1) |
| Time (days) since last PRBC transfusion to Visit 2 (Week 0) | n | 29 | 15 | 44 |
| | Mean (SD) | 69.1 (56.79) | 57.8 (45.36) | 65.3 (52.91) |
| Hb concentration (g/dL) | n | 35 | 18 | 53 |
| | Mean (SD) | 9.392 (1.4024) | 8.676 (0.7749) | 9.149 (1.2646) |
| Reticulocyte count (cells × $10^9$/L) | n | 35 | 18 | 53 |
| | Mean (SD) | 230.190 (80.9842) | 180.278 (109.0530) | 213.239 (93.5182) |
| LDH concentration (U/L) | n | 35 | 18 | 53 |
| | Mean (SD) | 2150.95 (909.420) | 1945.94 (1003.733) | 2081.32 (937.942) |
| Haptoglobin concentration (g/L) | n | 35 | 18 | 53 |
| | Mean (SD) | 0.079 (0.0024) | 0.080 (0.0000) | 0.080 (0.0019) |
| Total bilirubin concentration (µmol/L) | n | 35 | 18 | 53 |
| | Mean (SD) | 39.365 (20.4550) | 35.527 (15.0411) | 38.061 (18.7324) |
| Platelet count (cells × $10^9$/L) | n | 35 | 18 | 53 |
| | Mean (SD) | 191.41 (118.663) | 125.53 (51.126) | 169.04 (105.135) |

| | | | | |
|---|---|---|---|---|
| PNH Type II and Type III RBCs (%) | n | 35 | 18 | 53 |
| | Mean (SD) | 43.572 (24.5337) | 38.848 (22.4308) | 41.967 (23.7306) |
| PNH Type II RBCs (%) | n | 35 | 18 | 53 |
| | Mean (SD) | 12.519 (17.5272) | 11.220 (17.4405) | 12.078 (17.3404) |
| PNH Type III RBCs (%) | n | 35 | 18 | 53 |
| | Mean (SD) | 31.053 (20.1578) | 27.628 (17.2910) | 29.890 (19.1339) |
| Percentage of FLAER-negative PNH granulocytes | n | 35 | 18 | 53 |
| | Mean (SD) | 67.6166 (20.59913) | 65.0004 (24.17127) | 66.7281 (21.67977) |
| Percentage of FLAER-negative PNH monocytes | n | 35 | 18 | 53 |
| | Mean (SD) | 94.9993 (5.37186) | 90.3883 (9.88122) | 93.4333 (7.45978) |
| Total FACIT-Fatigue Scale score | n | 35 | 16 | 51 |
| | Mean (SD) | 36.3 (10.66) | 37.1 (9.32) | 36.6 (10.17) |
| LASA total score | n | 35 | 16 | 51 |
| | Mean (SD) | 186.5 (59.12) | 193.8 (49.95) | 188.8 (56.01) |
| EORTC QLQ-C30 Global Health score | n | 35 | 16 | 51 |
| | Mean (SD) | 63.33 (19.723) | 61.98 (15.806) | 62.90 (18.436) |

Abbreviations: EDC = electronic data capture; EORTC = European Organisation for the Research and Treatment of Cancer; FACIT = Functional Assessment of Chronic Illness Therapy; FLAER = fluorescent aerolysin; ITT = intent-to-treat; LASA = Linear Analog Scale Assessment; LDH = lactate dehydrogenase; N = number of subjects in treatment group; n = number of subjects included in parameter; PRBC = packed red blood cell; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; SoC = standard of care.

Note: Baseline is defined as the average of measurements prior to the first dose of pegcetacoplan or on or prior to assignment to SoC treatment for efficacy endpoints during the screening period but as the last measurement before the first dose of pegcetacoplan or on or prior to assignment to SoC treatment for other endpoints.

[a] Number of transfusions is defined as the number of transfusion events regardless of PRBC units transfused.

[b] Reported in EDC data.

Source: Table 14.1.5.1.1.

Prior medications

Prior medications and procedures are defined as those the subject takes or undergoes within 28 days (or 2 years for documentation of vaccination) prior to the start of screening (Visit 1) until the first dose of study drug.

Medications were coded ATC class (ATC Level 2) and preferred term (ATC Level 5) using the World Health Organization Drug Dictionary Enhanced, Version 01 March 2019 (B3). The table below presents the prior medications used in ≥10% of subjects.

**Table 26: Prior Medications in ≥10% of Subjects (ITT Set)**

| ATC Level 2 Term | Pegcetacoplan (N = 35) | SoC (N = 18) | Total (N = 53) |
|---|---|---|---|
| Any previous medications, n (%) | 31 (88.6) | 16 (88.9) | 47 (88.7) |
| Antianemic preparations, n (%) | 28 (80.0) | 15 (83.3) | 43 (81.1) |
| Corticosteroids for systemic use, n (%) | 17 (48.6) | 5 (27.8) | 22 (41.5) |
| Vitamins, n (%) | 10 (28.6) | 6 (33.3) | 16 (30.2) |
| Antithrombotic agents, n (%) | 6 (17.1) | 5 (27.8) | 11 (20.8) |
| Mineral supplements, n (%) | 9 (25.7) | 1 (5.6) | 10 (18.9) |
| Antihistamines for systemic use, n (%) | 5 (14.3) | 4 (22.2) | 9 (17.0) |
| Drugs for acid related disorders, n (%) | 5 (14.3) | 4 (22.2) | 9 (17.0) |
| Diuretics, n (%) | 4 (11.4) | 3 (16.7) | 7 (13.2) |
| Agents acting on the renin-angiotensin system, n (%) | 4 (11.4) | 2 (11.1) | 6 (11.3) |
| Anabolic agents for systemic use, n (%) | 4 (11.4) | 2 (11.1) | 6 (11.3) |
| Calcium channel blockers, n (%) | 2 (5.7) | 2 (11.1) | 4 (7.5) |
| Antihypertensives, n (%) | 1 (2.9) | 2 (11.1) | 3 (5.7) |
| Sex hormones and modulators of the genital system, n (%) | 1 (2.9) | 2 (11.1) | 3 (5.7) |
| Beta blocking agents, n (%) | 0 | 2 (11.1) | 2 (3.8) |
| Lipid modifying agents, n (%) | 0 | 2 (11.1) | 2 (3.8) |

Abbreviations: ATC = Anatomical Therapeutic Chemical; ITT = intent-to-treat; N = number of subjects in treatment group; n = number of subjects; SoC = standard of care.
Source: Table 14.1.7.1.

## Outcomes and estimation

Efficacy was analysed in a hierarchical fashion, starting with the primary endpoints and then progressing stepwise through the secondary endpoints after statistical significance was reached for the primary endpoints. Additional secondary endpoints were also evaluated.

The secondary endpoints were evaluated in the order in which they had been presented in the SAP. The secondary endpoints are presented in the order in which they appear in the SAP until analysis of change from baseline to Week 26 in FACIT-Fatigue Scale score, at which point statistical significance was not met. After this, all remaining secondary and additional secondary endpoints are presented according to category.

Primary efficacy endpoints

*First co-primary endpoint: Hb stabilization*

Hb stabilization was defined as avoidance of a >1 g/dL decrease in Hb concentration from baseline in the absence of transfusion.

An ad hoc analysis was also performed using avoidance of >2 g/dL decrease in Hb concentration as a criterion for Hb stabilization.

**Table 27: Hb stabilization over 26 weeks**

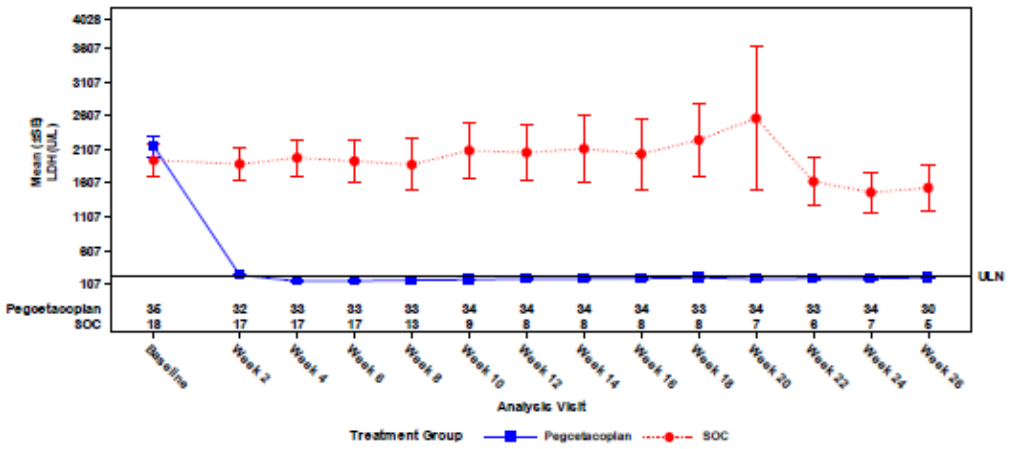
| | Pegcetacoplan group (N=35) | SoC group (N=18) | Adjusted difference |
|---|---|---|---|
| **Subjects with Hb stabilization as avoidance of a >1 g/dL decrease** | 30/35 (85.7%) | 0/18 (0%) | 0.7311 (95% CI 0.5720-0.8902) |
| | | | p-value <0.0001 |
| **Subjects with Hb stabilization as avoidance of a >2 g/dL decrease (ad hoc analysis)** | 31/35 (88.6%) | 0/18 (0%) | 0.7505 (95%CI, 0.5969-0.9041) |

*Second co-primary endpoint: change in LDH concentration from baseline to Week 26*

At Week 26 the least-square (LS) mean (SE) changes from baseline in LDH concentration were as follows:

- Pegcetacoplan group: –1870.47 (100.971)
- SoC group: –400.09 (312.988)

Mean (SE) observed LDH concentrations by treatment group during the RCP are plotted in the figure below.




Abbreviation: RCP = randomized controlled period; SoC = standard of Care; SE = standard error
Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC.
The normal range of central lactate dehydrogenase (U/L) is [113, 226]
SoC arm only includes data on or before escape.
Source: Appendix 16.2.6, Listing 16.2.6.3; Table 14.2.2.1.1; Figure 14.2.2.1.4.

**Figure 9. Mean (SE) LDH Concentration (U/L) Over Time by Treatment Group**

<u>Key secondary efficacy endpoints</u>

*Hb response*

An Hb response is defined as a ≥ 1 g/dL increase in Hb from baseline at Week 26.

At Week 26 the numbers of subjects with an Hb response were as follows:

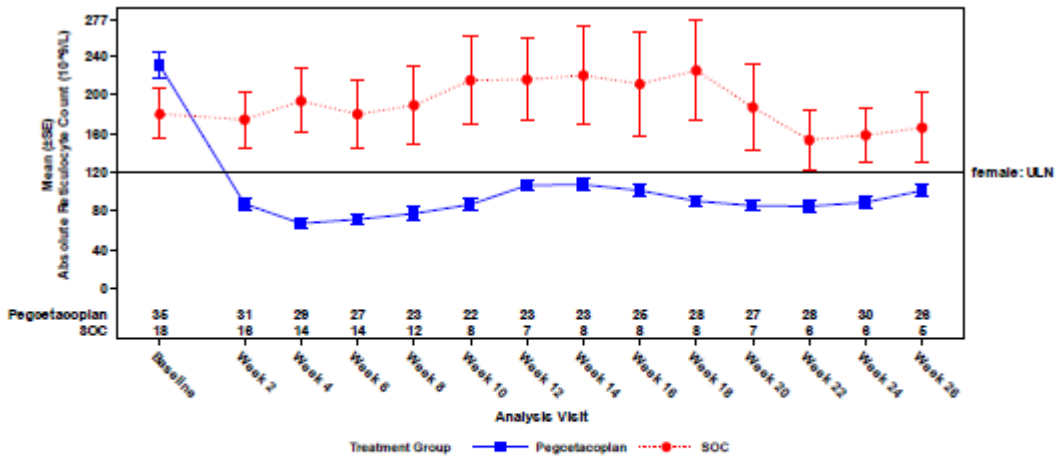
- pegcetacoplan group (N = 35): 25 subjects (71.4%)
- SoC group (N = 18): 1 subject (5.6%)

*ARC change from baseline*

During the RCP, the LS mean (SD) change from baseline in ARC was as follows:

- pegcetacoplan group (N = 35): –123.26 (9.164)
- SoC group (N = 15): –19.44 (25.209)

The mean (SE) observed ARC values over time by treatment group during the RCP are plotted in the figure below.




Abbreviation: ITT = Intent-To-Treat; RCP = randomized controlled period; SoC = standard of Care
Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC.
Absolute Reticulocyte Count normal range from central laboratory (cells × $10^9$/L) for Female is [10, 120].
Absolute Reticulocyte Count normal range from central laboratory (cells × $10^9$/L) for Male is [10, 140].
SoC arm only includes data on or before escape.
Source: Appendix 16.2.6, Listing 16.2.6.4; Table 14.2.3.1.1; Figure 14.2.3.4

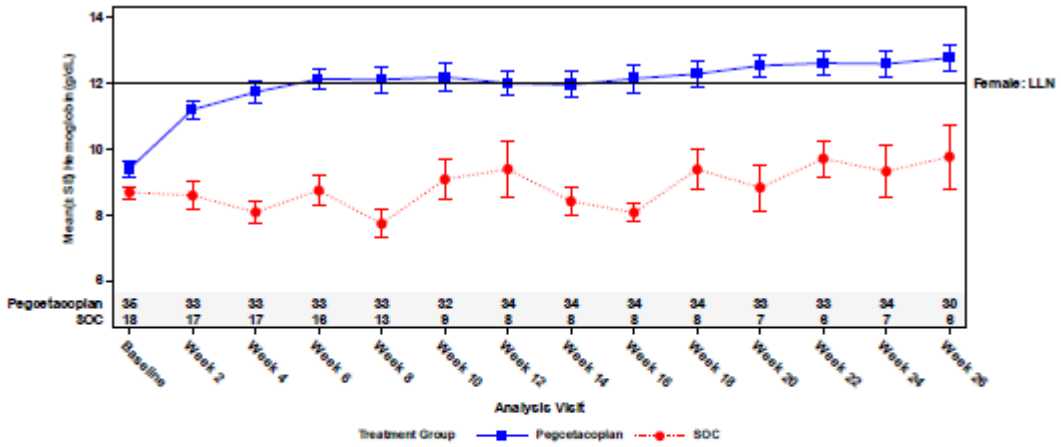
**Figure 10: Mean (SE) Absolute Reticulocyte Count (Cells × $10^9$/L) Over Time by Treatment Group During the RCP (ITT Set)**

*Hb change from baseline*

At Week 26 the LS mean (SE) changes from baseline in Hb concentration were as follows:

- pegcetacoplan group (N = 35): 2.94 (0.383)
- SoC group (N = 18): 0.27 (0.759)

Mean (SE) observed Hb concentrations over time during the RCP are plotted in the figure below.




Abbreviations: ITT = Intent-To-Treat, RCP = randomized controlled period, Hb = hemoglobin; SE = standard error; SoC = standard of care.
Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC.
Hb normal range from central laboratory (g/dL) for Female is [12, 16].
Hb normal range from central laboratory (g/dL) for Male is [13.6, 18].
Hb normal range for all local laboratories (g/dL) is [11.2, 18].
SoC arm only includes data on or before escape.
Source: Appendix 16.2.6, Listing 16.2.6.2; Table 14.2.1.1.1; Figure 14.2.1.1.4

**Figure 11: Mean (SE) Hb Concentration (g/dL) Over Time by Treatment Group During the RCP (ITT Set)**

Hb concentrations for the pegcetacoplan group reached LLN by Week 6 and were maintained at or above the LLN through Week 26. Hb concentrations for the SoC group stayed below the LLN throughout the RCP.

**Table 28: Transfusion or decrease Hb> 2g/dL, transfusion avoidance and number of PRBC units during the RCP**

| | **Pegcetacoplan group (N=35)** | **SoC group (N=18)** |
|---|---|---|
| **Number of subjects who received a transfusion or had a decrease of >2 g/dL from baseline Hb (n, %)** | 4 (11.4%) | 18 (100%) |
| | Adjusted difference: –0.7505 (95% CI,–0.9041 to –0.5969)<br>P-value <0.0001 | |
| **Number of subjects who avoided transfusion* (n, %)** | 32 subjects (91.4%) | 1 subject (5.6%) |
| | Adjusted difference: 0.7241 (95% CI, 0.5583-0.8899)<br>P-value <0.0001 | |
| **Median number of transfusion units** | 0.0 | 3.0 |
| | Adjusted median difference: 3.0 (95% CI, 2.0-4.0)<br>P-value <0.0001 | |

*Subjects who did not have a transfusion but withdrew before Week 26 or escaped from SoC to pegcetacoplan were not considered to have achieved transfusion avoidance.

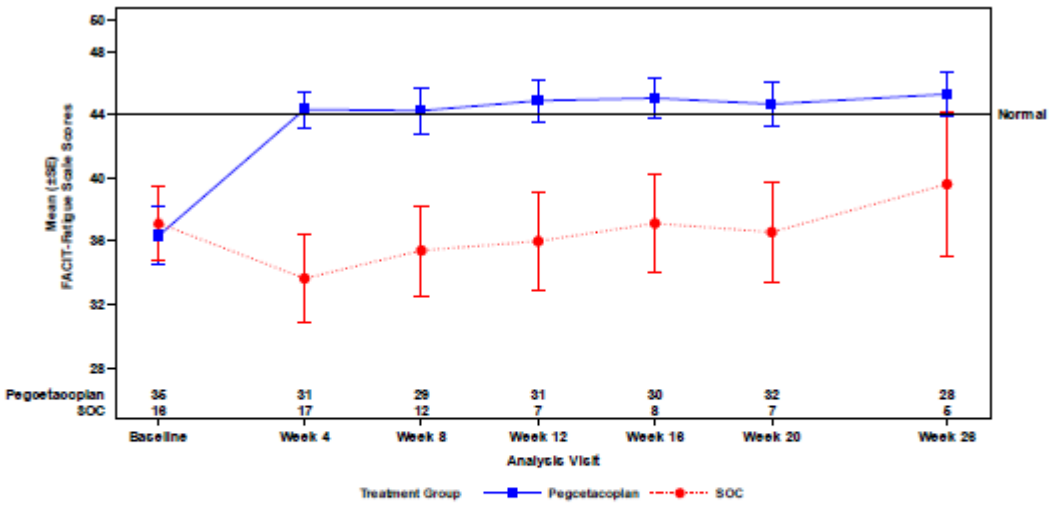
*FACIT-Fatigue Scale Score*

At Week 26 the improvement in FACIT-Fatigue Scale score, as shown in LS mean (SE) change from baseline, was clinically meaningful and numerically greater in the pegcetacoplan group than in the SoC group, as follows:

- pegcetacoplan group (N = 35): 7.78 (1.210)
- SoC group (N = 18): 3.26 (2.113)

The adjusted difference between pegcetacoplan and SoC was 4.51 (95%CI, –0.21 to 9.24), with a nominal P value of 0.0610.

The mean FACIT-Fatigue Scale scores over time by treatment group during the RCP are plotted in the figure below. FACIT-Fatigue Scale scores in subjects treated with pegcetacoplan rose to the normal range starting at Week 4 and were maintained throughout the RCP, and FACIT-Fatigue Scale scores for the SoC group remained below normal.




Abbreviations: FACIT = Functional Assessment of Chronic Illness Therapy; ITT = Intent-To-Treat; RCP = randomized controlled period; SE = standard error; SoC = standard of care
Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC.
Normal value is 44.
SoC arm only includes data on or before escape.
Source: Appendix 16.2.6, Listing 16.2.6.7.2, Table 14.2.8.1.1, Figure 14.2.7.3

**Figure 12: Mean (SE) FACIT-Fatigue Scale Scores Over Time by Treatment Group During the RCP (ITT Set)**

The table below presents the number and percentage of subjects achieving ≥3 points of improvement, which is generally considered clinically meaningful, in FACIT-Fatigue Scale scores from baseline during the RCP for the ITT set. All values after the ICEs were set to missing.

**Table 29: Number and Percentage of Subjects Achieving ≥3 Points of Improvement**

| Analysis visit | Score improvement ≥3 points change from baseline | Statistic | Pegcetacoplan (N = 35) | SoC (N = 18) |
|---|---|---|---|---|
| Week 4 | Yes | n (%) | 20 (57.1) | 2 (11.1) |
| | No | n (%) | 11 (31.4) | 15 (83.3) |
| Week 8 | Yes | n (%) | 21 (60.0) | 3 (16.7) |
| | No | n (%) | 8 (22.9) | 9 (50.0) |
| Week 12 | Yes | n (%) | 22 (62.9) | 1 (5.6) |
| | No | n (%) | 9 (25.7) | 6 (33.3) |
| Week 16 | Yes | n (%) | 21 (60.0) | 1 (5.6) |
| | No | n (%) | 9 (25.7) | 7 (38.9) |
| Week 20 | Yes | n (%) | 21 (60.0) | 1 (5.6) |
| | No | n (%) | 11 (31.4) | 6 (33.3) |
| Week 26 | Yes | n (%) | 21 (60.0) | 2 (11.1) |
| | No | n (%) | 7 (20.0) | 3 (16.7) |

Abbreviations: FACIT = Functional Assessment of Chronic Illness Therapy; ITT = intent-to-treat; RCP = randomized controlled period; n = number of subjects.
Data collected after a transfusion through Week 26 or escape from SoC to pegcetacoplan treatment group or withdraw from the study or lost to follow-up is excluded from analysis. Data collected after treatment discontinuation will be included in the analysis. However, if subjects discontinued study at the same date of treatment discontinuation, data collected after withdrawn from study will be excluded.
Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC.
This table summarizes data as observed with no imputation of missing data. All values after the ICEs were set to missing
Source: Appendix 16.2.6, Listing 16.2.6.7.3; Table 14.2.8.2.1.

*Normalization of Hb, ARC, and LDH at Week 26*

The most relevant analysis of normalization at Week 26 is described below.

**Table 30: Normalization of Hb, ARC and LDH at Week 26**

| | **Pegcetacoplan (N=35)** | **SoC (N=18)** | **Adjusted difference** |
|---|---|---|---|
| **Hb normalization** | 16/35 (45.7%) | 0/18 (0%) | 0.3645 (95%CI, 0.1648-0.5642) |
| **ARC normalization** | 21/35 (60.0%) | 1/18 (5.6%) | 0.4630 (95% CI, 0.2529-0.6750) |
| **LDH normalization** | 23/35 (65.7%) | 0/18 (0%) | 0.5592 (95%CI, 0.3682-0.7502) |

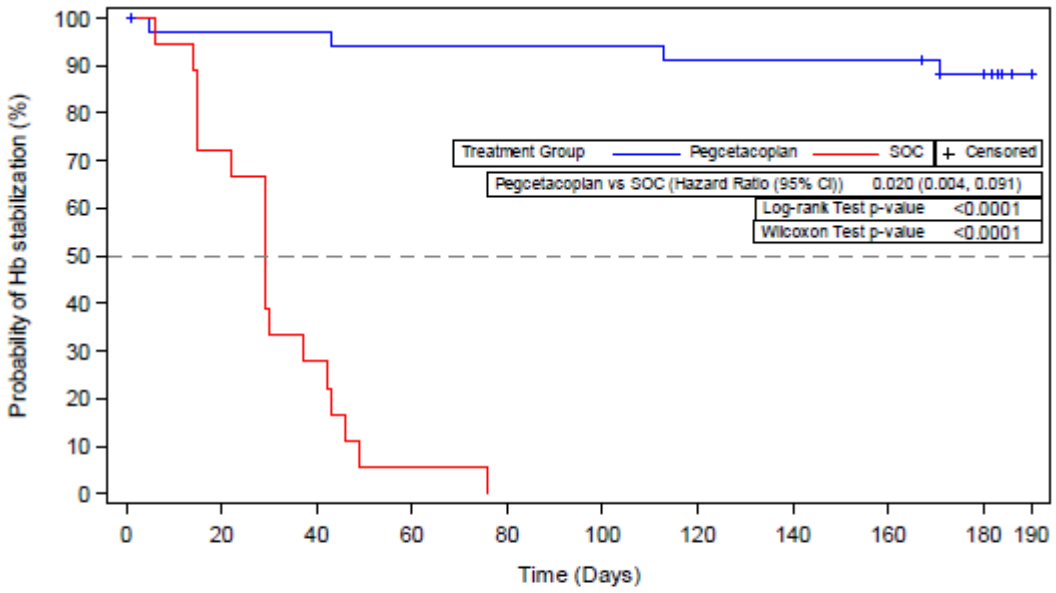
*Time to failure of Hb stabilization*

The figure and table below show the time to first Hb stabilization failure during the RCP for the ITT set.

**Table 31: Time to First Hb Stabilization Failure During the RCP (ITT Set)**

| | Pegcetacoplan (N = 35) | SoC (N = 18) |
|---|---|---|
| Number of subjects with failure of Hb stabilization, n (%) | 4 (11.4) | 18 (100) |
| Number of subjects censored, n (%)[a] | 31 (88.6) | 0 |
| Median time to first-on-study failure of Hb stabilization, weeks (95% CI) | – (– to –) | 4.143 (2.143, 5.286) |
| Stratified hazard ratio (pegcetacoplan vs SoC) | 0.020 | |
| 95% CI | 0.004, 0.091 | |

Abbreviations: Hb = hemoglobin; RCP = randomized controlled period; SoC = standard of care; ITT = intent-to-treat; n = number of subjects.
[a] For subject who were randomized but did not receive any treatment will be censored at the date of randomization. For subject who missed ≥3 consecutive visits will be censored at the visit before the first missing visit.
Hb stabilization is defined as avoidance of a >1 g/dL decrease in Hb concentrations from baseline through Week 26 in the absence of transfusion.
Transfusion refers to any transfusion of PRBC, LDPRC, LPPRC, LPRC, LPB, or whole blood.
Hazard ratio is based on Cox proportional hazards model.
– = Not Estimable
* significant at 0.05 α level.
Source: Appendix 16.2.6, Listing 16.2.6.2; Table 14.2.1.6.




Abbreviations: Hb = hemoglobin; ITT = intent-to-treat; RCP = randomized controlled period; SoC = standard of care
Hb stabilization is defined as avoidance of a >1 g/dL decrease in Hb concentrations from baseline through Week 26 in the absence of transfusion.
Transfusion refers to any transfusion of PRBC, LDPRC, LPPRC, LPRC, LPB, or whole blood.
Censored: For subject who randomized but did not receive any treatment will be censored at the date of randomization. For subject who missed ≥3 consecutive visits will be censored at the visit before the first missing visit.
Data after escape is excluded.
Source: Appendix 16.2.6, Listing 16.2.6.2; Table 14.2.1.6; Figure 14.2.1.6.1

**Figure 13: Time to First Hb Stabilization Failure During the RCP (ITT Set)**

*Time to PRBC transfusion during the RCP (ITT set)*

**Table 32: Time to PRBC Transfusion During the RCP (ITT Set)**

| | Pegcetacoplan (N = 35) | SoC (N = 18) |
|---|---|---|
| Number of subjects with PRBC transfusion, n (%) | 2 (5.7) | 13 (72.2) |
| Number of subjects censored, n (%)[a] | 33 (94.3) | 5 (27.8) |
| Median time to first-on-study PRBC transfusion (weeks) with 95% CI | – (–, –) | 7.0 (4.143, 10.286) |
| Stratified Hazard Ratio (pegcetacoplan vs SoC) | 0.025 | |
| 95% CI | 0.005, 0.121 | |

Abbreviations: PRBC = packed red blood cell; RCP = randomized controlled period; SoC = standard of care; ITT = intent-to-treat; n = number of subjects.

[a] The subjects who escape from SoC to peg will be censored at the date of escape. The subject who lost to follow-up or discontinue the study will be censored at the last visit. For subject who randomized but did not receive any treatment will be censored at the date of randomization. For subject who missed ≥ 3 consecutive visits will be censored at the visit before the first missing visit.

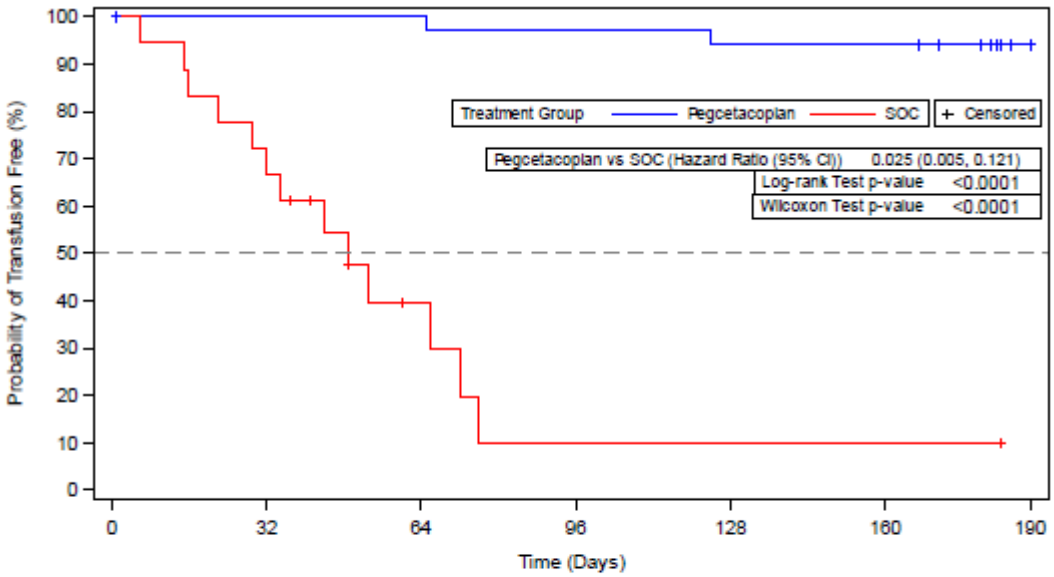
Transfusion refers to any transfusion of PRBC, LDPRC, LPPRC, LPRC, LPB, or whole blood.

Stratified by number of PRBC within 12 months prior to screening (<4, ≥4) reported in EDC data.

– = Not Estimable

*: significant at α 0.05.

Source: Appendix 16.2.6, Listing 16.2.6.1; Table 14.2.4.3.




Abbreviations: ITT = intent-to-treat; RCP = randomized controlled period; SoC = standard of care

SoC arm only includes data on or before escape.

Censored: The subjects who escape from SoC to peg will be censored at the date of escape. The subject who lost to follow-up or discontinue the study will be censored at the last visit. For subject who randomized but did not receive any treatment will be censored at the date of randomization. For subject who missed ≥3 consecutive visits will be censored at the visit before the first missing visit.

Transfusion refers to any transfusion of PRBC, LDPRC, LPPRC, LPRC, LPB, or whole blood.

Source: Appendix 16.2.6, Listing 16.2.6.1; Table 14.2.4.3; Figure 14.2.1.7

**Figure 14: Time to Transfusion During the RCP (ITT Set)**

*Other secondary efficacy endpoints at Week 26*

- Transfusion-free subjects

Subjects who did not receive a transfusion during the RCP are described as transfusion free.

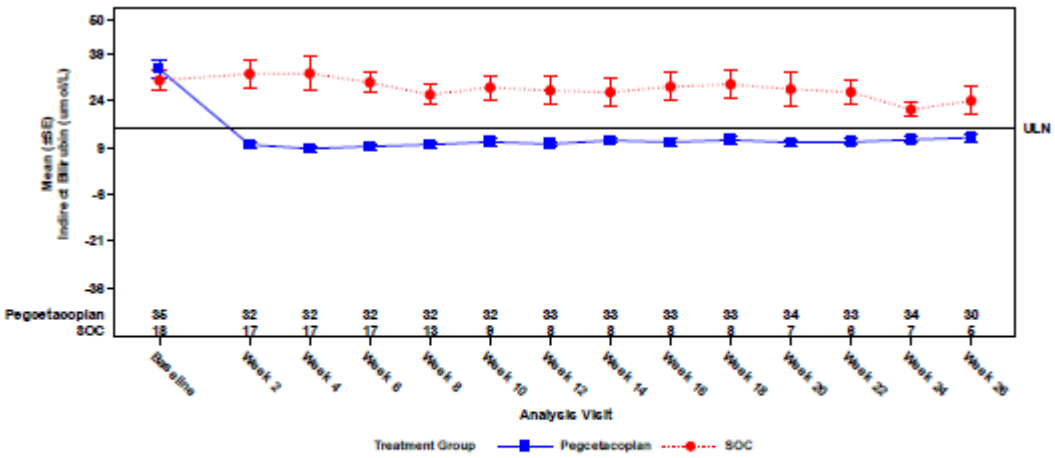
Subjects who had not had a transfusion but withdrew before Week 26 or had no transfusion before escape to pegcetacoplan were considered transfusion free

- Indirect Bilirubin Concentration at Week 26

The mean (SE) observed indirect bilirubin concentrations over time by treatment group during the RCP are plotted in the figure below Indirect bilirubin concentration in subjects treated with pegcetacoplan dropped to below the ULN starting at Week 2 and was maintained below the ULN throughout the RCP; subjects in the SoC group maintained indirect bilirubin levels above ULN throughout the RCP.

Samples for genotyping (for Gilbert syndrome) were obtained via buccal swab tests done at the screening visit. Four poor metabolizers were identified (3 were assigned to the pegcetacoplan group and 1 to the SoC group). Only one subject, who was in the pegcetacoplan group, reported Gilbert syndrome in their medical history. All 4 subjects had adequate responses in Hb and LDH concentration improvement. Three subjects had normalized bilirubin concentrations at Week 26.

The one subject who reported a medical history of Gilbert syndrome maintained high bilirubin levels during the study.

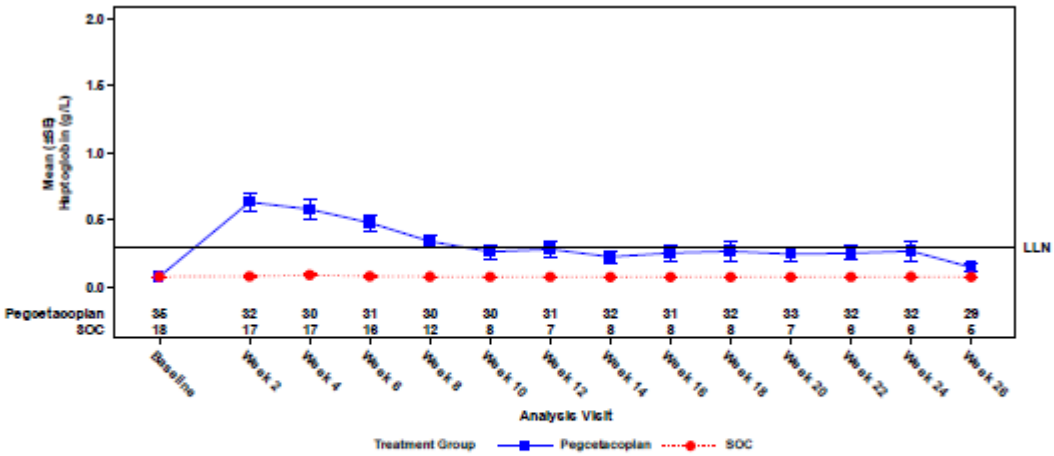



Abbreviations: ITT = intent-to-treat; RCP = randomized controlled period; SoC = standard of care; SE = standard error
Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC.
The normal range of central Indirect Bilirubin (µmol/L) is [1.7, 15.4]
SoC arm only includes data on or before escape.
Source: Appendix 16.2.6, Listing 16.2.6.5.2; Table 14.2.6.1; Figure 14.2.5.1.4

**Figure 15: Mean (SE) Indirect Bilirubin Concentration (µmol/L) Over Time by Treatment Group During the RCP (ITT Set)**

- Haptoglobin Concentrations at Week 26

The mean (SE) observed haptoglobin concentration over time by treatment group during the RCP is presented in the figure below. Haptoglobin concentrations in subjects treated with pegcetacoplan rose to above/around the LLN starting at Week 2 and remained there through Week 24; subjects in the SoC group maintained haptoglobin levels below LLN throughout the RCP.




Abbreviations: ITT = intent-to-treat; RCP = randomized controlled period; SoC = standard of care; SE = standard error
Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC.
The normal range of central Haptoglobin (g/L) is [0.3, 2]
SoC arm only includes data on or before escape.
Source: Appendix 16.2.6, Listing 16.2.6.6; Table 14.2.7.1; Figure 14.2.6.4

**Figure 16: Man (SE) observed haptoglobin concentration over time by treatment group during the RCP**

**Table 33: Tabulated view of other secondary endpoints at Week 26**

| | **Pegcetacoplan group (N=35)** | **SoC group(N=18)** |
|---|---|---|
| **Transfusion-free subjects** | 33/35 (94.3%) | 4/18 (22.2%) |
| | Adjusted difference: 0.6504 (95% CI, 0.4747-0.8260) | |
| **Change from baseline for indirect bilirubin concentration (LS mean [SE])** | -20.91 (1.376) | -5.28 (3.866) |
| | Difference: -15.63 (95% CI, -23.72 to – 7.53)* | |
| **Change from baseline of haptoglobin concentration (LS mean [SE])** | 0.11 (0.042) | 0.01 (0.054) |
| | Adjusted difference: 0.10 (95%CI, -0.04 to 0.23) | |

* Not adjusted

*Quality of life*

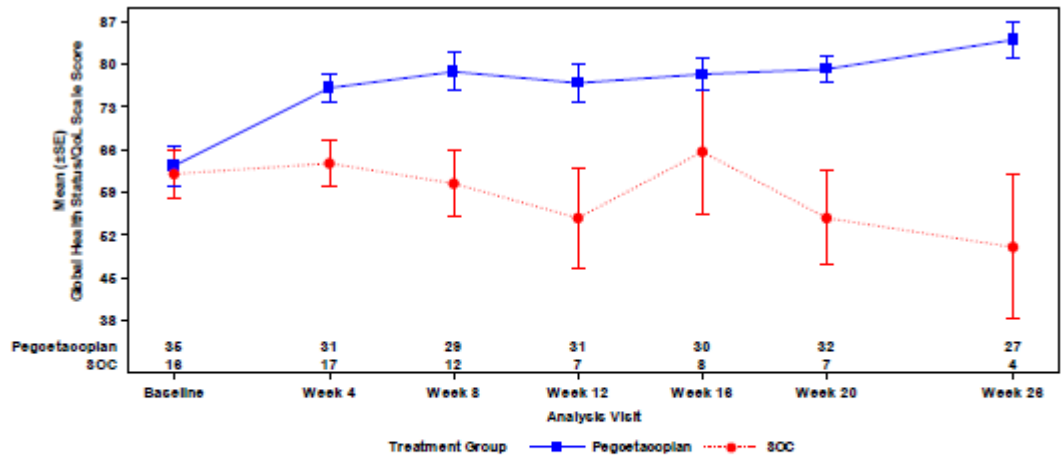
- EORTC QLQ-C30 Scores (version 3)

At Week 26 the LS mean (SE) changes (improvements) from baseline in EORTC QLC-C30 scores are as follows:

  - pegcetacoplan (N = 35): 18.90 (2.909)
  - SoC (N = 18): -2.85 (5.703)

The adjusted difference between pegcetacoplan and SoC was 21.75 (95% CI, 9.35-34.16).

The mean observed EORTC QLC-C30 Global Health Status/QoL Scale scores over time by treatment arm during the RCP are plotted in the figure below.




Abbreviations: EORTC = European Organisation for Research and Treatment of Cancer; ITT = intent-to-treat; QLQ-C30 = 30-item Core Quality of Life Questionnaire; RCP = randomized controlled period; SoC = standard of care; SE = standard error
Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC.
SoC arm only includes data on or before escape.
Source: Appendix 16.2.6, Listing 16.2.6.9.2; Table 14.2.10.1; Figure 14.2.9.2

**Figure 17: Mean (SE) EORTC QLQ-C30 Scores Over Time by Treatment Group During the RCP (ITT Set)**

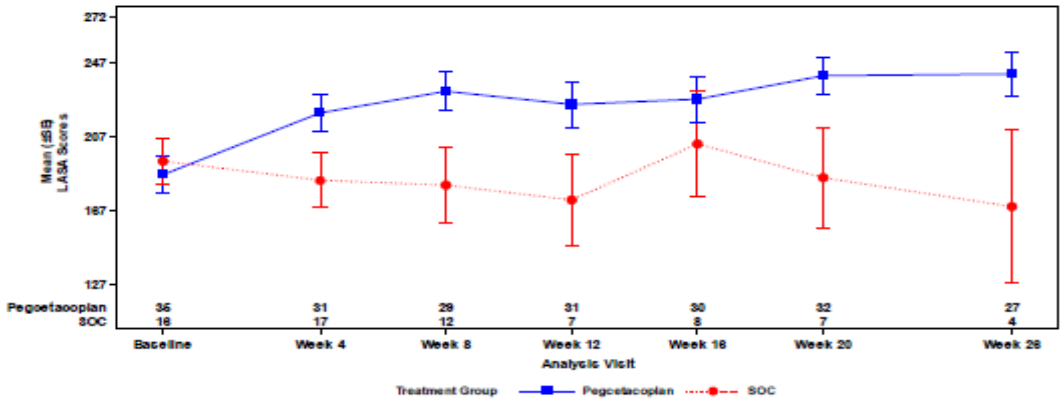
- LASA Scores

The LS mean (SE) LASA scores at Week 26 are as follows:

  - pegcetacoplan (N = 35): 50.39 (9.062)
  - SoC (N = 18): –5.39 (17.689)

The adjusted difference in LASA score improvement between pegcetacoplan and SoC was 55.79 (95% CI, 16.83-94.74).

The mean observed LASA scores over time by treatment group during the RCP are plotted in the figure below.




Abbreviations: LASA = Linear Analog Scale Assessment; ITT = intent-to-treat; RCP = randomized controlled period; SoC = standard of care; SE = standard error
Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC.
SoC arm only includes data on or before escape.
Source: Appendix 16.2.6, Listing 16.2.6.8.1; Table 14.2.9.1; Figure 14.2.8.3

**Figure 18: LASA Scores Over Time by Treatment Group During the RCP (ITT Set)**

*Time to escape from SoC to pegcetacoplan*

Eleven subjects (61.1%) escaped to pegcetacoplan. The median time to escape was 10.2 weeks (95% CI: 7.000-NA).

- ARC for subjects who escaped to pegcetacoplan

The observed ARCs and changes from baseline in ARC for subjects who escaped to pegcetacoplan during the RCP for the ITT set are presented in CSR, Table 14.2.3.1.2.2.

- Hb concentration for subjects who escaped to pegcetacoplan

The observed and change from baseline values for Hb concentration by analysis visit for subjects who escaped to pegcetacoplan during the RCP for the ITT set are presented in CSR, Table 14.2.1.1.2.2.

- LDH for subjects who escaped to pegcetacoplan

The observed and change from baseline values for LDH concentration by analysis visit for subjects who escaped to pegcetacoplan during the RCP for the ITT set are presented in CSR, Table 14.2.2.1.2.2.

Exploratory efficacy endpoints

*Breakthrough haemolysis*

Subjects with breakthrough haemolysis were defined as having at least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnoea], anaemia [Hb concentration <10 g/dL]; major adverse vascular events, including thrombosis; dysphagia; or erectile dysfunction) in the presence of elevated LDH concentration ≥2× the ULN after prior LDH concentration reduction to <1.5× the ULN on therapy.

The table below presents the proportion of subjects treated with pegcetacoplan who had any haemolytic event, sign, or symptom while LDH concentration was elevated (breakthrough haemolysis) in the pegcetacoplan groups.

**Table 34: Breakthrough Hemolysis in Subjects Treated with Pegcetacoplan (ITT Set)**

| | Pegcetacoplan | | |
|---|---|---|---|
| | Pegcetacoplan (N = 35) | SoC to pegcetacoplan (after escape) (N = 11) | Overall (N = 46) |
| **Any LDH elevated (2 × ULN), after prior reduction, n (%)** | | | |
| No | 31 (88.6) | 11 (100) | 42 (91.3) |
| Yes | 4 (11.4) | 0 | 4 (8.7) |
| **Any hemolytic event, sign, or symptom while LDH elevated (breakthrough hemolysis), n (%)** | | | |
| No | 33 (94.3) | 11 (100) | 44 (95.7) |
| Yes | 2 (5.7) | 0 | 2 (4.3) |

Abbreviations: LDH = lactate dehydrogenase; SoC = standard of care; ULN = upper limit of normal, n = number of subjects
Note: ULN = 226 U/L for all subjects. Elevated LDH is defined as LDH ≥2 × the ULN. LDH reduction is defined as LDH <1.5 × the ULN.
SoC to pegcetacoplan column only includes data for SoC subjects collected after escape to pegcetacoplan.
Source: Table 14.3.1.17.2.

- LDH concentrations

The table below presents the proportion of subjects in the SoC groups with haemolytic signs and symptoms while LDH concentration was elevated.

**Table 35: Elevated LDH Concentration with Hemolytic Signs and Symptoms During the RCP in the SoC Group (ITT Set)**

| | SoC | | |
|---|---|---|---|
| | SoC (N = 7) | SoC to pegcetacoplan prior to escape (N = 11) | Overall (N = 18) |
| **Any hemolytic event, sign, or symptom while LDH elevated, n (%)** | | | |
| No | 0 | 0 | 0 |
| Yes | 7 (100) | 11 (100) | 18 (100) |

Abbreviations: LDH = lactate dehydrogenase; RCP = randomized controlled period; SoC = standard of care; ULN = upper limit of normal, n = number of subjects
Note: ULN = 226 U/L for all subjects. Elevated LDH is defined as LDH ≥2 × the ULN.
SoC to pegcetacoplan column only includes data for SoC subjects collected on or prior to escape to pegcetacoplan.
Source: Table 14.3.1.17.3.

## Ancillary analyses

Sensitivity analysis of coprimary efficacy endpoints

No sensitivity analysis was performed for the first coprimary endpoint.

For the second coprimary endpoint, 2 types of sensitivity analyses were performed: MMRM and the tipping point imputation approach. Refer to the SAP in Appendix 16.1.9 for additional information about the sensitivity analyses.

**Table 36: Sensitivity Analysis (MMRM Method): Change from Baseline in LDH**

| Visit | Difference in LS mean | 95% CI | *P* value* |
|---|---|---|---|
| Week 2 | –1639.48 | –1995.07, –1283.89 | <.0001 |
| Week 4 | –1822.26 | –2177.51, –1461.01 | <.0001 |
| Week 6 | –1817.64 | –2173.43, –1461.86 | <.0001 |
| Week 8 | –1888.91 | –2252.86, –1524.96 | <.0001 |
| Week 10 | –1763.57 | –2141.20, –1385.94 | <.0001 |
| Week 12 | –1675.29 | –2058.31, –1292.28 | <.0001 |
| Week 14 | –1731.78 | –2114.79, –1348.76 | <.0001 |
| Week 16 | –1648.45 | –2031.47, –1265.44 | <.0001 |
| Week 18 | –1841.87 | –2225.21, –1458.54 | <.0001 |
| Week 20 | –2010.79 | –2399.87, –1621.71 | <.0001 |
| Week 22 | –1587.52 | –1985.26, –1189.77 | <.0001 |
| Week 24 | –1548.44 | –1937.92, –1158.96 | <.0001 |
| Week 26 | –1566.36 | –1976.95, –1155.77 | <.0001 |

Abbreviations: LS = Least-Square; MMRM = mixed-effects model for repeated measures; ITT = intent-to-treat.
* significant at 0.05 α level
Baseline is defined as average of measurements prior to first dose of pegcetacoplan or prior to randomization of SoC.
Model: change from baseline = treatment + baseline value + analysis visit + strata + analysis visit × Treatment, where strata is number of PRBC transfusions within the 12 months prior to Day –28 (<4; ≥4) reported in EDC data. All values after escape from SoC to pegcetacoplan were set to missing.
Source: Appendix 16.2.6, Listing 16.2.6.3; Table 14.2.2.2.1.

The MMRM sensitivity analysis confirmed that the difference between the pegcetacoplan and SoC groups in change from baseline in LDH concentration was statistically significant. Statistical significance was shown (P<.0001) at all time points from Week 2 to Week 26.

**Table 37: Sensitivity Analysis (MMRM Method): Change from Baseline in LDH**

| Analysis visit | Delta | Estimate of LS mean difference (pegcetacoplan -SoC) | 95% CI | *P* value |
|---|---|---|---|---|
| Week 26 | 600 | –844.23 | –1681.23, –7.24 | .0481* |
| | 650 | –794.23 | –1631.23, 42.76 | .0629 |

Abbreviations: LS = Least-Square; MMRM = mixed-effects model for repeated measures; ITT = intent-to-treat.
Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC.
Model: change from baseline = treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is number of PRBC transfusions within the 12 months prior to Day –28 (<4; ≥4) reported in EDC data.
Tipping point is the point in which the estimated difference between APL2 and SoC tipped from significant to nonsignificant. All values after escape from SoC to pegcetacoplan were set to missing.
*significant at 0.05 α level.
Delta is the values added to change from baseline at Week 26 for adjustment.
Source: Appendix 16.2.6, Listing 16.2.6.3; Table 14.2.2.4.1.

Sensitivity to departure from the MAR assumption was investigated by the tipping point imputation approach using the delta-adjusted stress testing method, which would find the level of deviation from MAR (delta) that would tip the finding from significant to nonsignificant.

The tipping point imputation sensitivity analysis showed that a delta of 650 (with LS mean difference of –794.23) would not meet statistical significance, and a delta of 600 (with LS mean difference of –844.23) would meet statistical significance. This result means that comparison in LDH concentration data between the pegcetacoplan and SoC group would only become nonsignificant if one assumed that

subjects who did not have their Week 26 assessments had an LDH value which was worse by 650 U/L or more than what would have been estimated under a MAR assumption. This level of worsening by 650 U/L or more in LDH value is not clinically plausible for the 5 subjects who were assigned to pegcetacoplan and needed imputation for the Week 26 LDH assessment. Therefore, the tipping point analysis corroborates and confirms the results of the primary endpoint analysis, which demonstrates that pegcetacoplan is superior to SoC in mean difference in change from baseline in LDH concentration.

Supportive analyses of primary efficacy endpoints

The first coprimary efficacy endpoint (Hb stabilization) was analyzed using logistic regression with the effects of treatment group and stratification factor included in the model using the ITT and PP sets.

The second coprimary efficacy endpoint (reduction in LDH concentration from baseline to Week 26) was analyzed using an ANCOVA model for the ITT set with an LOCF approach for handling missing data. The second coprimary efficacy endpoint was also analyzed using an ANCOVA model for the ITT and PP sets with a BOCF approach for handling missing data. Results are presented in CSR, Table 14.2.1.2.1;

The first supportive analysis evaluated Hb stabilization from baseline through Week 26 in the absence of transfusion in the ITT set using the exact logistic regression.

The results of the analysis were as follows:

- pegcetacoplan group (N = 35): 30 subjects (85.7%) achieved Hb stabilization
- SoC group (N = 18): no subjects achieved Hb stabilization

The unadjusted proportion difference (pegcetacoplan – SoC) was 85.7, and its P value was <0.0001. These results support the finding that more patients treated with pegcetacoplan than with SoC achieved Hb stabilization.

The second supportive analysis evaluated Hb stabilization from baseline through Week 26 in the absence of transfusion in the PP set using the exact logistic regression method.

The results of the analysis were as follows:

- pegcetacoplan group (N = 33): 29 subjects (87.9%) achieved Hb stabilization
- SoC group (N = 13): no subjects achieved Hb stabilization

The unadjusted proportion difference (pegcetacoplan – SoC) was 87.9, and its P value was <0.0001. This analysis demonstrates that the results from the PP set are consistent with those from the ITT set.

The third supportive analysis evaluated change from baseline at Week 26 in LDH concentration during the RCP using the ANCOVA method with LOCF for missing data in the ITT. All values after escape from SoC to pegcetacoplan were set to missing.

The LS mean (SD) values were as follows:

- pegcetacoplan group (N = 35): –1829.73 (172.998)
- SoC group (N = 18): 8.69 (238.981)

The difference between pegcetacoplan and SoC was –1838.43 (95% CI, –2435.60 to –1241.25), and its P value was <0.0001. These results are consistent with the second coprimary endpoint, which demonstrates that LDH concentrations are lower in the pegcetacoplan group than in the SoC group.

The fourth supportive analysis evaluated change from baseline at Week 26 in LDH concentration during the RCP using the ANCOVA method with BOCF for missing data in the ITT. All values after escape from SoC to pegcetacoplan were set to missing.

The LS mean (SD) values were as follows:

- pegcetacoplan group (N = 35): –1712.85 (113.329)
- SoC group (N = 18): –139.01 (156.553)

The difference between pegcetacoplan and SoC was –1573.84 (95% CI, –1965.04 to –1182.64), and its P value was <0.0001. These results are consistent with the second coprimary endpoint, which demonstrates that LDH concentrations are lower in the pegcetacoplan group than in the SoC group.

The fifth supportive analysis evaluated change from baseline at Week 26 in LDH (U/L) during the RCP using the ANCOVA method in the PP set.

All values after escape from SoC to pegcetacoplan were set to missing.

The LS mean (SD) values were as follows:

- pegcetacoplan group (N = 33): –1887.89 (129.680)
- SoC group (N = 13): –46.10 (495.458)

The difference between pegcetacoplan and SoC was –1841.79 (95% CI, –2839.91 to –843.67), and its P value was 0.0003. This demonstrate that the results from the PP set are consistent with those from the ITT set.

## *Summary of main study(ies)*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 38: Summary of efficacy for trial APL2-308**

| **Title: A Phase 3, Randomized, Multicenter, Open-Label, Controlled Study to Evaluate the Efficacy and Safety of APL-2 in Patients with Paroxysmal Nocturnal Haemoglobinuria (PNH)** | | | |
|---|---|---|---|
| Study identifier | Protocol code: APL2-308 ; US NCT number: NCT04085601 | | |
| Design | Phase 3, randomized, multicenter, open-label, controlled | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 26 weeks<br>up to 4 weeks<br>Ongoing, up to 36 weeks at DCO |
| Hypothesis | Superiority | | |
| Treatments groups | Pegcetacoplan | | 1080 mg SC twice weekly or every 3 days if needed until Week 26<br>35 patients randomized |
| | SoC excluding complement inhibitors | | Any supportive therapy deemed necessary until Week 26<br>18 patients randomized |
| Endpoints and definitions | Co-Primary endpoint | Hb stabilization | Proportion of subjects with avoidance of a >1 g/dL decrease in Hb concentration from baseline in the absence of transfusion |
| | Co-Primary endpoint | Change in LDH concentration | Change in LDH concentration from baseline to Week 26 |
| | Key Secondary endpoint | Hb response | Proportion of subjects with a ≥1g/dL increase in Hb from Baseline to Week 26 in the absence of transfusions |

| | | | |
|---|---|---|---|
| | Key Secondary endpoint | Change in ARC | Change from Baseline to Week 26 in ARC |
| | Key Secondary endpoint | Change in Hb level | Change from Baseline to Week 26 in Hb level |
| | Key Secondary endpoint | Transfusion rate | Proportion of subjects who received transfusion or had decrease of Hb > 2 g/dL from Baseline to Week 26 |
| | Key Secondary endpoint | Transfusion avoidance | Proportion of subjects who do not require a transfusion during the RCP |
| | Key Secondary endpoint | Number of transfusions | Number of packed red blood cell (PRBC) units transfused from Baseline to Week 26 |
| | Key Secondary endpoint | Change in FACIT-Fatigue Scale score | Change from Baseline to Week 26 in FACIT-Fatigue Scale score |
| Database lock | 05 August 2021 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population | Intent to treat (ITT) : all randomized subjects | | |
| Descriptive statistics and estimate variability | Treatment group | Pegcetacoplan | SoC |
| | Number of subjects, N | 35 | 18 |
| | Hb stabilization<br>n: number of subjects with event (%) | 20 (85.7%) | 0 (0%) |
| | Change in LDH concentration<br>Least-square (LS) mean changes ± standard error (SE) | -1870 ± 100.971 | -400.09 ± 312.988 |
| | Hb response, n (%) | 25 (71.4%) | 1 (5.6%) |
| | Change in ARC<br>LS mean change ± standard deviation (SD) | -123.26 ± 9.164 | -19.44 ± 25.209 |
| | Change in Hb level<br>LS mean change ± SE | 2.94 ± 0.383 | 0.27 ± 0.75 |
| | Transfusion rate, n (%) | 4 (11.4%) | 18 (100%) |
| | Transfusion avoidance, n (%) | 32 (91.4%) | 1 (5.6%) |
| | Median number of transfusions | 0.0 | 3.0 |
| **Effect estimate per comparison** | **Endpoints** | **Comparison groups: Pegcetacoplan vs SoC** | |
| | Hb stabilization | Proportion of subjects | 0.857 |
| | | 95% CI | (0.5720,0.8902) |
| | | P-value | <0.0001 |
| | Change in LDH | Difference | -1470.38 |

| | | | |
|---|---|---|---|
| | | 95% CI | –2113.44 to –827.32 |
| | | P-value | <0.0001 |
| | Hb response | Adjusted difference | 0.5411 |
| | | 95% CI | (0.3390, 0.7431) |
| | | P-value | <0.0001 |
| | Change in ARC | Adjusted difference | -103.82 |
| | | 95% CI | (-158.90, -48.74) |
| | | P-value | <0.0002 |
| | Change in Hb level | Adjusted difference | 2.67 |
| | | 95% CI | (0.99, 4.35) |
| | | P-value | <0.0019 |
| | Transfusion need | Adjusted difference | 0.7505 |
| | | 95% CI | (-0.9041, -0.5969) |
| | | P-value | <0.0001 |
| | Transfusion avoidance | Adjusted difference | 0.7241 |
| | | 95% CI | (0.5583, 0.8899) |
| | | P-value | <0.0001 |
| | Median number of transfusions | Adjusted median difference | 3.0 |
| | | 95% CI | (2.0, 4.0) |
| | | | |
| | | P-value | <0.0001 |

## 2.4.2. Discussion on clinical efficacy

Pegcetacoplan is approved in EU under the tradename Aspaveli to treat adult patients with paroxysmal nocturnal haemoglobinuria (PNH) anaemic after at least 3 months of C5 inhibition therapy. This variation application is based on the efficacy and safety results from Study APL2-308 to cover the following indication: treatment of adult patients with PNH who have haemolytic anaemia.

The study was GCP-compliant and at the time of submission, no GCP inspection had been requested nor taken place and no inspection was planned.

No scientific advice has been sought for this application.

No dose-response study nor supportive studies have been provided in this application.

**Main study**

Study design

Study APL2-308 was a Phase 3, randomized, multicenter, open-label and controlled study to evaluate the efficacy and safety of pegcetacoplan in adult subjects with PNH who are complement-naïve or have not recently receive complement therapy.

Enrolled subjects received either (ratio 2:1) pegcetacoplan or standard of care (SoC) excluding complement inhibitors consisting of supportive therapies that only treat the symptoms but do not affect the course of the disease and therefore are not standard of care.

During the 26-week randomized controlled period (RCP), any patient in the SoC group with a decrease in haemoglobin of at least 2 g/dL from baseline or a thromboembolic event (TE) secondary to PNH had the option of an early escape therapy with pegcetacoplan. The duration of RCP and availability of an escape arm are endorsed, as it was confirmed in response to RSI that escaping to pegcetacoplan arm did not affect the interpretation of efficacy results.

Eligible patients were then included in an open-label extension study (Study APL2-307). Otherwise, follow-up visits were performed (8-week follow-up).

Treatment was to be administered as follows:

**Pegcetacoplan group**: 1080 mg subcutaneous (SC) twice weekly. A dose adjustment to 1080 mg SC every 3 days was allowed if a subject has a lactate dehydrogenase (LDH) level greater than 2 x upper limit of normal (ULN), as indicated in the approved SmPC.

**SoC group**: any supportive therapy deemed necessary by the investigator such as transfusions, erythropoietin or immunosuppressants, systemic corticosteroids, vitamin K antagonists, iron, B13 or B9 supplementation and/or heparin.

Considering that the co-primary endpoints are objective and that different types of treatments (such as transfusions) were used as a comparator, the open-label design is acceptable. However, the absence of blinding is a limitation, especially when assessing quality of life.

Since pegcetacoplan was compared with the suboptimal control, the defined small sample size seems sufficient to detect a clinically relevant difference in the primary outcomes with 90% power at the 5% level of significance.

The unavailability of C5 inhibitors worldwide is acknowledged but the absence of use of eculizumab or ravulizumab as an active comparator is not optimal in terms of efficacy and safety since subjects from the target population have access to C5 inhibition therapy as current SoC in the EU. However, as pivotal study can be regarded as a placebo controlled and as studied population might reflect complement inhibitor-naïve PNH population, it was accepted considering that the Applicant adequately managed to justify similarity between EU and non-EU complement inhibitor-naïve, i.e. extrapolation of the data from non-EU to EU target population.

The similarity between both populations was confirmed in terms of race and the other relevant PK/PD aspects. Indirect comparisons were made with complement inhibitor-naïve subjects from the ravulizumab pivotal study and complement inhibitor-experienced subjects treated with pegcetacoplan. These cross-study comparisons are subject to interpretation but were considered acceptable by CHMP.

Population

Overall, eligibility criteria were acceptable, limiting inclusion to PNH subjects with anaemia and active haemolysis while addressing the risks associated with pegcetacoplan treatment (e.g., hypersensitivity, vaccination requirements and increased susceptibility to infections).

The study locations included 22 sites which are outside of the EU (and hence not representative for the current treatment of PNH) the ethics committees in two European countries (Poland and Serbia) approved participation in the study but not a single participant was enrolled.

Out of 68 screened patients, 15 (22.06%) were screen failures. Of the 53 randomised participants, 35 were randomized to pegcetacoplan and 18 to the SoC group.

Two subjects in the pegcetacoplan group and 1 subject in the SoC group withdrew from the study. Among those 3 subjects, 2 had TEAEs leading to death (1 in each arm), the third patient (pegcetacoplan group) was lost to follow-up.

Thirty-three subjects (94.3%) in the pegcetacoplan group and 6 (33.3%) subjects in the SoC group completed the 26-week treatment period. The proportion of participants completing Week 26 is low in the control group is small as 11 (61.1%) participants escaping to pegcetacoplan escape arm, which is ethically justifiable. All 50 subjects (from pegcetacoplan, pegcetacoplan escape and control arms) opted to enter the extension study (Study APL2-307).

Demographic characteristics were overall reasonably balanced among treatment arms. The mean age was 44.5 years, with slightly more male patients were included, mean. Mean weight and height were rather small for an adult population (63.7 kg and 163.8 cm, respectively). There were no participants of White race. Patients included were mostly Asian (65.7% in the treatment group vs. 88.9% in the control group) or American Indian/Alaska Native (25.7% and 11.1%). The Applicant provided PK/PD arguments supporting that the study sample is representative for the target population in terms of race. All study subjects were complement inhibitor-naïve.

Baseline disease characteristics were reasonably well balanced in both treatment arms. The included participants were diagnosed with PNH approximately 5.5 years prior to inclusion, received approximately 4.5 PRBC transfusions in the 12 months prior to screening, had a baseline Hb concentration of approximately 9g/dL, an elevated absolute reticulocyte count (approximately 213 cellsx$10^9$/L), elevated LDH concentration (2081 U/L), low haptoglobin (approximately 0.08 g/L) and elevated total bilirubin (approximately 38 lμmol/L)). Those characteristics are typical of active haemolytic anaemia.

Treatments

As requested in RSI, a list of all concomitant medications given to patients at the investigator's discretion during the study for both treatment groups was provided. With the exception of iron supplements, vitamin B12 and folic acid, the following medications were used: prednisolone, dexamethasone, oxymetholone, danazol, cyclophosphamide, omeprazole, tranexamic acid, rivaroxaban, acetylsalicylic acid, filgrastim, granulocyte colony-stimulating factor, packed RBC transfusion, other transfusions, epoetin alfa, ascorbic acid. These supportive therapies are not considered to have affected the study results. The timing of the vaccination is not in line with the approved SmPC, which recommends vaccination 2 weeks prior to starting therapy but this will not be further pursued.

Compliance was high in both treatment arms throughout the randomized period, which is important considering the small sample size.

Endpoints

The conceptual framework of this study is superiority over SoC for the primary and secondary outcomes. It is noted that the comparator was not deemed optimal according to the EU standards.

Hb stabilization (defined as a ≥1 g/dL Hb decrease at Week 26) and reduction in LDH concentration from baseline to Week 26 had been chosen as co-primary efficacy endpoints for this study. These endpoints are clinically meaningful for assessing the effect of pegcetacoplan on haemolytic anaemia.

No less than 14 secondary endpoints were presented and evaluated in a hierarchical order, which is endorsed, all focused on anaemia and haemolysis management: monitoring of Hb and LDH at different time points as well as changes from baseline in Hb, LDH, absolute reticulocyte count (ARC) and transfusion need. Quality of life was measured using the FACIT -fatigue scale, EORTC QLQ -C30 and the Linear Analog Scale Assessment (LASA).

Total bilirubin and indirect bilirubin are haemolytic biomarkers and were assessed as an additional secondary endpoint.

The proportion of patients with breakthrough haemolysis has exploratory value.

Haptoglobin concentration is not listed in the order of secondary endpoints. As explained by the Applicant, listing 'haptoglobin concentration' as one of the secondary endpoints in the CSR of Study 308 was overlooked. However, this was a pre-defined secondary endpoint introduced in the first version of the SAP (dated 03 March 2021). Indeed, haptoglobin concentration is mentioned as a

secondary endpoint in the provided SAP (version 3.0), although the exact timing when this endpoint was added could not be verified since earlier versions of the SAP are not provided (nor a summary of changes made with each version of the SAP). Nevertheless, results of haptoblogin were collected from the beginning of the study and are presented in Results section of Study APL2-308 CSR.

Overall from a clinical point of view, this approach is considered acceptable and relevant to explore the effects of pegcetacoplan treatment on the most common and disabling manifestations of PNH.

Statistical Plan

The ITT set included all randomised participants in the pegcetacoplan arm (35) and all randomised participants in the SoC arm (18), which is endorsed.

The applicant performed a review after entering all data into the database to define analysis sets and data issues (e.g., missing values, withdrawals, protocol deviations). The applicant did not specify what exactly was done in SAP after all the data had been entered into the database, but it was stated that the definition of the ITT set was predefined. Considering that the number of protocol deviations and withdrawals was low and balanced between the groups, this review should not have a significant impact on the overall evaluation. In addition, the second coprimary efficacy endpoint (reduction in LDH concentration) was extensively analysed in the CSR, taking into account different scenarios for missing values. All analyses were consistent with the primary analysis and confirmed superiority of pegcetacoplan to SoC. Furthermore, the efficacy of pegcetacoplan in PNH patients was already established during the initial MAA.

The sensitivity analyses for the second co-primary endpoint were performed using MMRM and the tipping point imputation approach.

Multiplicity was accounted for by a hierarchical testing of coprimary and secondary endpoints, which is endorsed.

Conduct

The rate of protocol deviations was similar between the pegcetacoplan and SoC groups (91.4% and 94.4% respectively), as well as the rate of major protocol deviations (37.1% and 33.3%). The majority of those deviations included study assessments and procedures with two subjects who received pegcetacoplan every 3 days instead of twice weekly. These protocol deviations are not expected to affect the completeness, accuracy, and reliability of the study data. Three subjects did not receive transfusion even though they met the criteria, but in the opinion of the investigator, this was not considered to compromise subject safety.

In addition, 5 subjects (4 subjects in the pegcetacoplan group and 1 subject who switched to pegcetacoplan) had a major protocol deviation related to study drug noncompliance. Reported missed doses had a transient and limited impact on Hb and LDH levels in the absence of confounding factors (medullary aplasia).

The protocol was modified three times during the study. In the first amendment, the definition of the primary endpoints was changed, normalization of Hb levels was added as a secondary endpoint, and the secondary objectives were reorganized. In addition, stratification at randomization, BMI as an inclusion criterion, and criteria for escape therapy were changed. The most notable changes in the second protocol amendment were the deletion of the secondary objective (change in Hb from baseline to week 26), the LDH criterion for dose increase, and a typo in the PRBC transfusion stratification categories. The changes in protocol amendment 3 were not significant. The protocol amendments, particularly the reordering of the hierarchically tested outcomes once the start of study has commenced, are not endorsed. Though these changes of secondary endpoints appear undoubtedly

relevant, it cannot be ruled out they were data-driven. Indeed, in an open-label trial, unmasked data are available at any time and can be source of potential updates jeopardizing the robustness of conclusion. Therefore claims were limited to the key secondary variables as planned in the first active version of the protocol.

**Efficacy data and additional analyses**

Co-primary endpoints

The first co-primary efficacy endpoint was Hb stabilization, defined as avoidance of a >1 g/dL Hb decrease at Week 26. The proportion of subjects with Hb stabilization was 85.7% in the pegcetacoplan group (adjusted difference: 0.7311 [95% CI 0.5720-0.8902]; p-value <0.0001) compared to 0% the SoC group, demonstrating the superiority of pegcetacoplan treatment over SoC in stabilizing Hb concentration over 26 weeks. This was further supported by an ad hoc analysis: Hb stabilization was defined as avoidance of a >2 g/dL Hb decrease, which represented 88.6% of subjects from the pegcetacoplan group (adjusted difference: 0.7505 [95% CI, 0.5969-0.9041]).

Change in LDH concentration from baseline to Week 26 was the second primary endpoint. The difference between the pegcetacoplan and SoC groups was –1470.38 (95% CI, –2113.44 to –827.32) with a P value of <0.0001, demonstrating the superiority of pegcetacoplan over SoC in controlling intravascular haemolysis (IVH) reflected by the decrease in LDH concentrations.

Secondary endpoints

Point of statistical significance was also met for the following key secondary endpoints:

- The proportion of subjects with Hb response (≥ 1 g/dL increase in Hb from baseline) at Week 26 was 71.4% in the pegcetacoplan group compared to 5.6% (adjusted difference: 0.5411 [95% CI, 0.3390-0.7431]; p-value <0.0001).
- The adjusted difference of the least-square (LS) mean change from baseline in ARC at Week 26 was –103.82 (95% CI, –158.90 to –48.74), with a p-value of 0.0002.
- The adjusted difference of the LS mean change from baseline in Hb at Week 26 was 2.67 g/dL (95% CI, 0.99-4.35).
- At Week 26, 11.4% of subjects who initially received pegcetacoplan had a transfusion or an Hb decrease of >2 g/dL from baseline compared 100% in the SoC group. Consistently, 32 subjects (91.4%) of the treatment group avoided transfusion vs. 1 subject (5.6%) in the SoC group. The median number of transfusion units in this group was 3.0 in the SoC group.

Mean FACIT-Fatigue Scale score in subjects receiving pegcetacoplan increased from baseline to normal levels at week 4 and remained slightly above the normal level up to week 26. The score was lower in the comparator arm and below the normal level during the entire 26 weeks, but with overlap of scores at week 26, due to which superiority was not demonstrated. Formal testing stopped at this point and all remaining secondary and additional secondary endpoints are considered exploratory.

Hb normalisation, LDH normalisation and ARC normalisation at week 26 were achieved in a numerically higher number of participants treated with pegcetacoplan then in patients in the comparator arm.

Time to failure of Hb stabilisation was not reached in pegcetacoplan arm while being 4 weeks in the comparator arm.

Time to first PBRC transfusion was 7 weeks in the comparator arm while it was not estimable in pegcetacoplan arm due to a small number of events.

The number of transfusion free subjects was greater for pegcetacoplan compared to comparator arm (94.3% vs 22.2%, respectively).

At week 26 the mean CFB for indirect bilirubin levels was numerically larger in pegcetacoplan compared to the comparator arm (-20.01 vs -5.28 µmol/L, respectively).

Starting from week 2, haptoglobin concentration was higher in pegcetacoplan compared to the control arm until week 26 of treatment.

Quality of life endpoints

EORTC QLC-C30 Global Health Status/QoL Scale scores in subjects treated with pegcetacoplan increased throughout the RCP starting at Week 4 while the scores of subjects in the SoC group showed a small decrease over time.

Subjects treated with pegcetacoplan demonstrated improvements in LASA scores throughout the RCP starting at Week 4; the scores of subjects in the SoC group varied but eventually showed a numerically small decline at Week 26.

Additional and exploratory endpoints

Hb stabilisation (defined as avoidance of a decrease of >2 g/dL from baseline in Hb concentration in the absence of transfusion) through Week 26 was achieved in more subjects in pegcetacoplan compared to comparator arm (88.6% vs 0, respectively).

Eleven out of 18 patients (i.e. 61.1%) in the SoC arm escaped to pegcetacoplan, after a median of 10 weeks. After treatment with pegcetacoplan commenced, efficacy results (CFB in ARC, CFB in Hb concentration, CFB in LDH concentrations) in the escape arm are consistent with the data from the pegcetacoplan arm.

As an exploratory endpoint, the proportion of participants experiencing breakthrough haemolysis during treatment with pegcetacoplan was small (2 out of 46, i.e. 4.3%). In comparison, all 18 participants from the SoC group had signs and symptoms of breakthrough haemolysis as defined previously.

In conclusion, the examined co-primary and the first 6 secondary endpoints (in the hierarchical testing procedure) demonstrated clear superiority of pegcetacoplan over the comparator arm. However, this has to be interpreted with caution in the context of substandard and only symptomatic treatment options offered in the so-called ‘standard of care’ arm and potentially data-driven reorganization of the efficacy endpoints.

## 2.4.3. Conclusions on the clinical efficacy

Overall, the main efficacy results presented were clinically meaningful, supporting the effectiveness of pegcetacoplan treatment in controlling haemolysis and correcting overly active haematopoiesis caused by anaemia over SoC (complement inhibitors excluded).

Section 5.1 of the SmPC has been updated to include the study results.

## 2.5. Clinical safety

### Introduction

Pegcetacoplan was first approved in the European Union for treatment of adult patients with PNH who become anaemic after treatment with a C5i for at least 3 months, at a dosage of 1080 mg by sc infusion twice weekly via a commercially available pump. The primary safety results presented in the initial marketing application included 4 studies in subjects with PNH: 1 pivotal Phase 3 controlled study (Study APL2-302's randomized controlled period in C5 inhibitor-treated subjects with PNH) and 3 supportive studies. Of the supportive studies, 2 studies included subjects not being treated with eculizumab, who are hereafter referred to as complement inhibitor naïve subjects (Study APL2-CP-PNH-204 and Study APL2-202), and 1 study included subjects treated with eculizumab (Study APL CP0514), who are hereafter referred to as complement inhibitor-experienced subjects.

From a safety point of view, the main issue at the time of initial MAA was that there was a limited database in terms of number of PNH patients exposed and in terms of duration of exposure, especially in setting of concerned indication with chronic use. The most prominent adverse events were **diarrhoea** and various **infusion site reactions** that were observed in much higher frequencies in pegcetacoplan group compared to eculizumab group in randomised controlled portion of the pivotal study. Number of **discontinuations** was not negligible, with clinically significant events of **haemolysis** that led to pegcetacoplan or study discontinuation. **Immunogenicity** has been added as an important potential risk in the updated EU RMP and has been included as a safety concern to be monitored in the PASS. **Serious infections** have been added as important potential risk in the RMP with additional risk mitigation measure using registry data. **Malignancies** and **haematological abnormalities** are also added as important potential risk in the RMP. **Additional long-term safety data** are still needed to better characterise the safety profile of pegcetacoplan (added as missing information in the RMP).

**Long-term PEG accumulation** has been added as an important potential risk in the RMP as requested and an endpoint to monitor this potential risk has been added to the post-authorisation safety study (PASS) using the International PNH Interest Group (IPIG) registry. A PASS using registry data, study APL2-302 and study 307 will investigate the important potential risk of serious hypersensitivity reactions, intravascular haemolysis after drug discontinuation, immunogenicity, malignancies and haematologic abnormalities and potential long-term effects of PEG accumulation.

Post-authorisation, the Applicant submitted a Type II Variation (EMEA/H/C/005553/II/0002) to provide the final results from Study APL2-302 48-week study data. These data established that the overall safety profile during the 48-week study **remained similar** to what had been observed in the pegcetacoplan group during the 16-week RCP.

Current **updated version of Summary of Clinical Safety** includes the results of another Phase 3 study, Study APL2-308, "A Phase 3, Randomized, Multicenter, Open-Label, Controlled Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients with PNH." Study APL2-308 included subjects who were not being treated with a complement inhibitor. The Applicant did not integrate the data from the two Phase 3 clinical studies, Study APL2-302 and Study APL2-308, because of differences in study design and duration of treatment between the two studies. **Summary tabulations** presenting TEAEs and SAEs from studies APL2-308, APL2-302, APL2-202, APL2-CP-PNH-204 and APL-CP0514 are submitted. They are supporting SmPC section 4.8 proposed changes. For study APL2-308, data locked as of 05 August 2021 were used. For study APL2-302, data locked as of 06 November 2020 were used. For study 204, data locked as of 21 January 2020 were used. For study

202, data locked as of 07 February 2020 were used. For study 0514, data locked as of 16 April 2019 were used.

**Additional safety data** are included from an ongoing long-term extension study (Study APL2-307) and an ongoing study in paediatric subjects with PNH (Study APL2-PNH-209). The data cut-off date is 13 November 2022 for the overall exposure to the drug as well as for the related SAEs and deaths reported in the ongoing long-term extension Study APL2 307 and the ongoing paediatric Study APL2-PNH-209. The data cut-off date is 15 April 2022 for the other safety events reported in the ongoing Study APL2 307 (ie, SAEs and discontinuation due to AEs). For the ongoing study in PNH, APL2-307, safety data (SAEs, related SAEs, deaths, and discontinuations due to AEs) are presented for completeness. There were no SAEs or deaths reported for Study APL2-PNH-209.

For study APL2-302, the 48-week data as of final database lock was on 06 November 2020 were already assessed during the initial MA assessment and the Aspaveli type II variation EMEA/H/C/005553/II/0002. Only new safety data within the assessment report, and the overall discussion and conclusion on the pegcetacoplan clinical safety profile are going to be presented.

## *Patient exposure*

**Table 39: Pegcetacoplan exposure in PNH studies**

| Category/study | Number of subjects with ≥1 pegcetacoplan dose | Number of subjects by duration of exposure (n) | | | | | | Cumulative years on pegcetacoplan |
|---|---|---|---|---|---|---|---|---|
| | | >6 mos | >1 yrs | >2 yrs | >3 yrs | >4 yrs | >5 yrs | |
| Exposure by study for completed and ongoing PNH studies (SC) | | | | | | | | |
| Study APL2-302 | 80 | 75 | 66 | 57 | 27 | 0 | 0 | 188.3 |
| Study APL2-202 | 4 | 4 | 4 | 4 | 4 | 1 | 0 | 15.8 |
| Study APL2-CP-PNH-204 | 22 | 18 | 18 | 14 | 14 | 11 | 0 | 65.0 |
| Study APL-CP0514 | 9 | 6 | 4 | 4 | 4 | 3 | 1 | 20.3 |
| Study APL2-308 | 52 | 50 | 49 | 42 | 1 | 0 | 0 | 116.4 |
| Study APL2-PNH-209[a] | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 3.5 |
| Cumulative | 170 | 156 | 144 | 121 | 50 | 15 | 1 | 409.3 |

Abbreviations: mos = months; PNH = paroxysmal nocturnal hemoglobinuria; SC = subcutaneous; yrs = years.
[a] Ongoing study.
Note: Exposure in the long-term safety study, Study APL2-307, is included in the parent study.
Source: Section 8.1, Pegcetacoplan SC Duration of Exposure (as of 13 November 2022).

**Table 40: Exposure of Pegcetacoplan During the Whole Study (Safety Set)**

| | | Pegcetacoplan | |
|---|---|---|---|
| | Statistic | Pegcetacoplan (N = 35) | SoC to pegcetacoplan (N = 11) |
| **Total dose exposed (mg)** | | | |
| | Mean (SD) | 76,618.3 (35,615.87) | 53,312.7 (34,456.14) |
| | Median | 57,240.0 | 43,200.0 |
| | Min, Max | 1080, 143640 | 11,880, 126360 |
| **Duration of treatment (days)** | | | |
| | Mean (SD) | 244.8 (113.93) | 168.5 (107.16) |
| | Median | 183.0 | 133.0 |
| | Min, Max | 1, 463 | 36, 385 |
| **Subjects with temporary infusion interruption** | n (%) | 1 (2.9) | 0 |
| **Number of infusions received** | | | |
| | Mean (SD) | 70.9 (32.98) | 49.4 (31.90) |
| | Median | 53.0 | 40.0 |
| | Min, Max | 1, 133 | 11, 117 |
| **Total number of infusions** | M | 2483 | 543 |
| Infusions completed | m (%) | 2481 (99.92) | 543 (100) |
| Infusion interrupted | m (%) | 2 (0.08) | 0 |

Abbreviation: SoC = standard of care, n = number of subjects; SD = standard deviation; m = number of events, M = total number of events.
Duration of treatment (days) = last date of infusion - first date of infusion + 1
m (%) = m/M x100.
Source: Appendix 16.2.5, Listing 16.2.5.1; Table 14.1.9.1.2.

Baseline characteristics were consistent for studies including PNH subjects who were C5i-treated and who were C5i-naïve.

**Table 41: Subject Demographic and Baseline Characteristics from Study APL2-308 (Safety Set)**

| Parameter | Statistic | Pegcetacoplan (N = 35) | SoC (N = 18) | Total (N = 53) |
|---|---|---|---|---|
| Sex<br>Female<br>Male | n (%) | <br>16 (45.7)<br>19 (54.3) | <br>8 (44.4)<br>10 (55.6) | <br>24 (45.3)<br>29 (54.7) |
| Age (years) | Mean (SD) | 42.2 (12.70) | 49.1 (15.64) | 44.5 (14.00) |
| Body weight (kg) | Mean (SD) | 65.08 (13.28) | 61.08 (9.92) | 63.72 (12.29) |
| Height (cm) | Mean (SD) | 164.52 (7.63) | 162.44 (7.73) | 163.82 (7.65) |
| Body mass index (kg/m$^2$) | Mean (SD) | 24.00 (4.43) | 23.07 (2.94) | 23.68 (3.98) |
| **Race** | n (%) | | | |
| Asian | | 23 (65.7) | 16 (88.9) | 39 (73.6) |
| Black or African American | | 2 (5.7) | – | 2 (3.8) |
| Native Hawaiian/other Pacific Islander | | – | – | – |
| Maori | | – | | – |
| White | | – | – | – |
| American Indian or Alaska Native | | 9 (25.7) | 2 (11.1) | 11 (20.8) |
| Other | | 1 (2.9) | – | 1 (1.9) |
| **Ethnicity** | n (%) | | | |
| Hispanic or Latino | | 12 (34.3) | 2 (11.1) | 14 (26.4) |
| Not Hispanic or Latino | | 23 (65.7) | 16 (88.9) | 39 (73.6) |
| Years since PNH diagnosis | Mean (SD) | 5.66 (5.92) | 5.49 (5.15) | 5.60 (5.62) |
| Number of transfusions in the 12 months prior to screening | Mean (SD) | 3.9 (4.37) | 5.1 (4.98) | 4.3 (4.57) |
| Hb level (g/dL) at baseline | Mean (SD) | 9.56 (1.36) | 8.48 (1.05) | 9.20 (1.35) |
| LDH level (U/L) at baseline | Mean (SD) | 2100.0 (890.13) | 1857.1 (994.68) | 2017.5 (924.66) |

Abbreviations: CSR = clinical study report; Hb = hemoglobin; LDH = lactate dehydrogenase; N = number of subjects in each group or population; n = number of subjects in each category; PNH = paroxysmal nocturnal hemoglobinuria; RCP = randomized controlled period; SoC = standard of care.

Notes: The total treatment period comprised the 26-week RCP and the post-RCP period in which subjects remained in the study until they rolled over into an open-label extension study. During the post-RCP period, subjects received pegcetacoplan or SoC per their treatment assignment, totaling up to 62 weeks of treatment. At any point during the study, any subject assigned to the SoC (excluding complement inhibitors) treatment arm who had an Hb concentration ≥2 g/dL below baseline or who presented with a qualifying thromboembolic event secondary to PNH was offered early escape therapy with pegcetacoplan. Pegcetacoplan dosage could be increased to 1080 mg every 3 days if clinically indicated. Subjects were naive to C5 inhibitor treatment. A dash signifies that the parameter or statistic was equal to 0 or was not determined in this study.

Sources: Study APL2-308 CSR, Table 14.1.4.2.1, Table 14.1.5.3.1.

The study APL2-308 safety set included all subjects who received at least 1 dose of study medication:

- pegcetacoplan (N = 35)
- SoC to pegcetacoplan (N = 11)
- overall pegcetacoplan, which included both the pegcetacoplan and SoC to pegcetacoplan groups (N = 46)
- subjects who were assigned to SoC (N = 18)

Subjects were analysed according to the treatment they received.

**Table 42: Subject Disposition in Study APL2-308 (Safety Set)**

| | Pegcetacoplan (N = 35) n (%) | SoC[a] (N = 18) n (%) | Total (N = 53) n (%) |
|---|---|---|---|
| Completed study | 33 (94.3) | 17 (94.4) | 50 (94.3) |
| Completed the study before COVID-19 pandemic | 1 (2.9) | 1 (5.6) | 2 (3.8) |
| Completed the study during COVID-19 pandemic | 32 (91.4) | 16 (88.9) | 48 (90.6) |
| Withdrawn from study | 2 (5.7) | 1 (5.6) | 3 (5.7) |
| Primary reason for withdrawal from study | | | |
| Adverse event | 0 | 0 | 0 |
| Lost to follow-up | 1 (2.9) | 0 | 1 (1.9) |
| Withdrawal by subject | 0 | 0 | 0 |
| Study termination by sponsor | 0 | 0 | 0 |
| Physician decision | 0 | 0 | 0 |
| Protocol violation | 0 | 0 | 0 |
| Death | 1 (2.9) | 1 (5.6) | 2 (3.8) |
| COVID-19 pandemic | 0 | 0 | 0 |
| Other | 0 | 0 | 0 |

Abbreviations: CSR = clinical study report; N = number of subjects in each group or population; n = number of subjects in each category; PNH = paroxysmal nocturnal hemoglobinuria; RCP = randomized controlled period; SoC = standard of care.

[a] Includes 11 subjects who escaped to pegcetacoplan and completed the study.

Notes: The total treatment period comprised the 26-week RCP and the post-RCP period in which subjects remained in the study until they rolled over into an open-label extension study. During the post-RCP period, subjects received pegcetacoplan or SoC per their treatment assignment, totaling up to 62 weeks of treatment. At any point during the study, any subject assigned to the SoC (excluding complement inhibitors) treatment arm who had a hemoglobin concentration ≥2 g/dL below baseline or who presented with a qualifying thromboembolic event secondary to PNH was offered early escape therapy with pegcetacoplan. Pegcetacoplan dosage could be increased to 1080 mg every 3 days if clinically indicated. Subjects were naïve to C5 inhibitor treatment.

Source: Study APL2-308 CSR, Table 14.1.2.2.

## Dose modifications

All subjects started pegcetacoplan at a dosage of 1080 mg subcutaneously twice weekly.

LDH concentration was monitored as part of the scheduled assessments at the planned clinic visits. After Visit 4 (Week 4), for any subject receiving pegcetacoplan, if LDH concentration was >2x the ULN on one occasion, a pegcetacoplan dosage increase to 1080 mg every third day could be considered.

- Two subjects (1 each in the pegcetacoplan and SoC to pegcetacoplan groups) were assigned in error the dosage of every 3 days instead of twice weekly without clinical justification and agreement by the sponsor's medical monitor. These were protocol deviations.
- The dosages for 3 subjects (2 in the pegcetacoplan group and 1 in the SoC to pegcetacoplan group) were increased to every 3 days after events of haemolysis deemed not related to pegcetacoplan during the post-RCP period. There were no other dose adjustments.

## *Adverse events*

Overview of treatment-emergent adverse events (TEAEs)

**Table 43: Overview of Treatment-Emergent Adverse Events During the Whole Study (Safety Set)**

| | Overall pegcetacoplan (N = 46) | SoC (while on SoC) (N = 18) |
|---|---|---|
| **Any TEAEs, n (%)** | 35 (76.1) | 12 (66.7) |
| Total events, m | 264 | 32 |
| **TEAEs by closest relationship to pegcetacoplan, n (%)** | | |
| Related | 16 (34.8) | |
| **TEAEs by closest relationship to infusion, n (%)** | | |
| Related | 12 (26.1) | |
| **TEAEs by maximum severity, n (%)** | | |
| Mild | 12 (26.1) | 7 (38.9) |
| Moderate | 17 (37.0) | 3 (16.7) |
| Severe | 6 (13.0) | 2 (11.1) |
| **Any injection site reaction, n (%)** | | |
| Yes | 16 (34.8) | |
| **Serious TEAEs** | 6 (13.0) | 3 (16.7) |
| Total events | 8 | 10 |
| **Serious TEAEs by closest relationship to pegcetacoplan, n (%)** | | |
| Related | 0 | |
| **TEAEs leading to pegcetacoplan discontinuation, n (%)** | 0 | |
| **TEAEs leading to death, n (%)** | 1 (2.2) | 1 (5.6) |

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event; m = number of events; n = number of subjects; SoC = standard of care.
A treatment-emergent adverse event is defined as an adverse event that starts on or after the first dose of investigational product for APL2 group, on or after randomization date for SoC group.
Any AEs with a missing or unknown severity are considered as severe.
If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count and all occurrences are counted each time in the total events count. All TEAEs are presented only once in the total unique events count.
Definitely related and possibly related AEs are classified as related AEs, and unlikely related and not related AEs are classified as unrelated AEs. AE with unknown relationship to study drug is counted as related AE in the table.
Any AE that occurred on or prior to escape event is counted in the SoC column, and after escape event is counted in the SoC to pegcetacoplan column.
A subject will be classified as having injection site reaction if the subject has at least one injection site reaction.
Overall pegcetacoplan refers to subjects who have received pegcetacoplan at any point during the study.
Source: Appendix 16.2.7, Listing 16.2.7.1; Table 14.3.1.1.3.

- TEAEs

The table below presents TEAEs by SOC and PT during the whole study.

**Table 44: Treatment-Emergent Adverse Events in any Treatment Group by System Organ Class and Preferred Term During the Whole Study (safety set)**

| | | Pegcetacoplan | | | SOC | | |
|---|---|---|---|---|---|---|---|
| System Organ Class/ Preferred Term | Statistics | Pegcetacoplan (N=35) | SOC to Pegcetacoplan (After Escape) (N=11) | Overall (N=46) | SOC (Prior to escape) (N=11) | SOC (Remain) (N=7) | SOC (While on SOC) (N=18) |
| Number of subjects with at least one TEAE | n (%) | 29 (82.9) | 6 (54.5) | 35 (76.1) | 7 (63.6) | 5 (71.4) | 12 (66.7) |
| General disorders and administration site conditions | n (%) | 15 (42.9) | 4 (36.4) | 19 (41.3) | 0 | 1 (14.3) | 1 (5.6) |
| Pyrexia | n (%) | 3 (8.6) | 1 (9.1) | 4 (8.7) | 0 | 0 | 0 |
| Injection site bruising | n (%) | 1 (2.9) | 1 (9.1) | 2 (4.3) | 0 | 0 | 0 |
| Injection site haemorrhage | n (%) | 0 | 2 (18.2) | 2 (4.3) | 0 | 0 | 0 |
| Injection site swelling | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Peripheral swelling | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Vaccination site pain | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Fatigue | n (%) | 1 (2.9) | 0 | 1 (2.2) | 0 | 1 (14.3) | 1 (5.6) |
| Malaise | n (%) | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (5.6) |
| Skin and subcutaneous tissue disorders | n (%) | 11 (31.4) | 1 (9.1) | 12 (26.1) | 0 | 0 | 0 |
| Ecchymosis | n (%) | 3 (8.6) | 0 | 3 (6.5) | 0 | 0 | 0 |
| Erythema | n (%) | 3 (8.6) | 0 | 3 (6.5) | 0 | 0 | 0 |
| Rash | n (%) | 1 (2.9) | 1 (9.1) | 2 (4.3) | 0 | 0 | 0 |
| Rash maculo-papular | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Infections and infestations | n (%) | 10 (28.6) | 1 (9.1) | 11 (23.9) | 2 (18.2) | 3 (42.9) | 5 (27.8) |
| Viral infection | n (%) | 3 (8.6) | 0 | 3 (6.5) | 0 | 0 | 0 |
| COVID-19 | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Helicobacter gastritis | n (%) | 0 | 1 (9.1) | 1 (2.2) | 0 | 0 | 0 |
| Oesophageal candidiasis | n (%) | 0 | 1 (9.1) | 1 (2.2) | 0 | 0 | 0 |
| Septic shock | n (%) | 1 (2.9) | 0 | 1 (2.2) | 0 | 1 (14.3) | 1 (5.6) |
| Upper respiratory tract infection | n (%) | 1 (2.9) | 0 | 1 (2.2) | 1 (9.1) | 1 (14.3) | 2 (11.1) |
| Herpes virus infection | n (%) | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (5.6) |
| Influenza | n (%) | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (5.6) |
| Pneumocystis jirovecii pneumonia | n (%) | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (5.6) |
| Pulmonary tuberculosis | n (%) | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (5.6) |
| Urinary tract infection | n (%) | 0 | 0 | 0 | 1 (9.1) | 1 (14.3) | 2 (11.1) |
| Metabolism and nutrition disorders | n (%) | 9 (25.7) | 2 (18.2) | 11 (23.9) | 3 (27.3) | 0 | 3 (16.7) |
| Hypokalaemia | n (%) | 4 (11.4) | 2 (18.2) | 6 (13.0) | 2 (18.2) | 0 | 2 (11.1) |
| Hypophosphataemia | n (%) | 1 (2.9) | 1 (9.1) | 2 (4.3) | 0 | 0 | 0 |
| Hyperuricaemia | n (%) | 1 (2.9) | 0 | 1 (2.2) | 1 (9.1) | 0 | 1 (5.6) |
| Dehydration | n (%) | 0 | 0 | 0 | 1 (9.1) | 0 | 1 (5.6) |
| Metabolic acidosis | n (%) | 0 | 0 | 0 | 1 (9.1) | 0 | 1 (5.6) |
| Blood and lymphatic system disorders | n (%) | 8 (22.9) | 2 (18.2) | 10 (21.7) | 2 (18.2) | 1 (14.3) | 3 (16.7) |
| Anaemia | n (%) | 2 (5.7) | 1 (9.1) | 3 (6.5) | 1 (9.1) | 0 | 1 (5.6) |
| Haemolysis | n (%) | 2 (5.7) | 1 (9.1) | 3 (6.5) | 0 | 0 | 0 |
| Thrombocytopenia | n (%) | 3 (8.6) | 0 | 3 (6.5) | 0 | 1 (14.3) | 1 (5.6) |
| Neutropenia | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Bone marrow failure | n (%) | 1 (2.9) | 0 | 1 (2.2) | 1 (9.1) | 0 | 1 (5.6) |
| Febrile neutropenia | n (%) | 1 (2.9) | 0 | 1 (2.2) | 0 | 1 (14.3) | 1 (5.6) |
| Musculoskeletal and connective tissue disorders | n (%) | 10 (28.6) | 0 | 10 (21.7) | 1 (9.1) | 0 | 1 (5.6) |
| Pain in extremity | n (%) | 6 (17.1) | 0 | 6 (13.0) | 0 | 0 | 0 |
| Arthralgia | n (%) | 5 (14.3) | 0 | 5 (10.9) | 0 | 0 | 0 |
| Musculoskeletal pain | n (%) | 3 (8.6) | 0 | 3 (6.5) | 0 | 0 | 0 |
| Back pain | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Plantar fasciitis | n (%) | 0 | 0 | 0 | 1 (9.1) | 0 | 1 (5.6) |
| Gastrointestinal disorders | n (%) | 7 (20.0) | 2 (18.2) | 9 (19.6) | 2 (18.2) | 0 | 2 (11.1) |
| Abdominal pain | n (%) | 2 (5.7) | 1 (9.1) | 3 (6.5) | 0 | 0 | 0 |
| Abdominal pain upper | n (%) | 1 (2.9) | 2 (18.2) | 3 (6.5) | 1 (9.1) | 0 | 1 (5.6) |
| Diarrhoea | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Gastritis | n (%) | 1 (2.9) | 1 (9.1) | 2 (4.3) | 0 | 0 | 0 |
| Nausea | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Dyspepsia | n (%) | 1 (2.9) | 0 | 1 (2.2) | 1 (9.1) | 0 | 1 (5.6) |
| Respiratory, thoracic and mediastinal disorders | n (%) | 8 (22.9) | 1 (9.1) | 9 (19.6) | 1 (9.1) | 3 (42.9) | 4 (22.2) |
| Cough | n (%) | 3 (8.6) | 0 | 3 (6.5) | 0 | 0 | 0 |
| Epistaxis | n (%) | 3 (8.6) | 0 | 3 (6.5) | 0 | 0 | 0 |
| Dyspnoea | n (%) | 1 (2.9) | 0 | 1 (2.2) | 0 | 1 (14.3) | 1 (5.6) |
| Oropharyngeal discomfort | n (%) | 1 (2.9) | 0 | 1 (2.2) | 0 | 1 (14.3) | 1 (5.6) |
| Oropharyngeal pain | n (%) | 0 | 1 (9.1) | 1 (2.2) | 0 | 0 | 0 |
| Rhinitis allergic | n (%) | 1 (2.9) | 0 | 1 (2.2) | 1 (9.1) | 0 | 1 (5.6) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rhinorrhoea | n (%) | 0 | 1 (9.1) | 1 (2.2) | 0 | 0 | 0 |
| Respiratory failure | n (%) | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (5.6) |
| Nervous system disorders | n (%) | 6 (17.1) | 2 (18.2) | 8 (17.4) | 0 | 0 | 0 |
| Dizziness | n (%) | 4 (11.4) | 1 (9.1) | 5 (10.9) | 0 | 0 | 0 |
| Headache | n (%) | 3 (8.6) | 1 (9.1) | 4 (8.7) | 0 | 0 | 0 |
| Somnolence | n (%) | 3 (8.6) | 0 | 3 (6.5) | 0 | 0 | 0 |
| Aphonia | n (%) | 0 | 1 (9.1) | 1 (2.2) | 0 | 0 | 0 |
| Investigations | n (%) | 6 (17.1) | 1 (9.1) | 7 (15.2) | 0 | 0 | 0 |
| Blood creatinine increased | n (%) | 2 (5.7) | 1 (9.1) | 3 (6.5) | 0 | 0 | 0 |
| Activated partial thromboplastin time prolonged | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Alanine aminotransferase increased | n (%) | 1 (2.9) | 1 (9.1) | 2 (4.3) | 0 | 0 | 0 |
| Blood creatine phosphokinase increased | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Renal and urinary disorders | n (%) | 4 (11.4) | 1 (9.1) | 5 (10.9) | 1 (9.1) | 0 | 1 (5.6) |
| Polyuria | n (%) | 2 (5.7) | 0 | 2 (4.3) | 0 | 0 | 0 |
| Dysuria | n (%) | 0 | 1 (9.1) | 1 (2.2) | 0 | 0 | 0 |
| Acute kidney injury | n (%) | 0 | 0 | 0 | 1 (9.1) | 0 | 1 (5.6) |
| Injury, poisoning and procedural complications | n (%) | 4 (11.4) | 0 | 4 (8.7) | 0 | 1 (14.3) | 1 (5.6) |
| Skin abrasion | n (%) | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (5.6) |
| Hepatobiliary disorders | n (%) | 1 (2.9) | 1 (9.1) | 2 (4.3) | 0 | 0 | 0 |
| Bile duct stone | n (%) | 0 | 1 (9.1) | 1 (2.2) | 0 | 0 | 0 |
| Vascular disorders | n (%) | 1 (2.9) | 1 (9.1) | 2 (4.3) | 0 | 0 | 0 |
| Hypertension | n (%) | 0 | 1 (9.1) | 1 (2.2) | 0 | 0 | 0 |
| Hypotension | n (%) | 0 | 1 (9.1) | 1 (2.2) | 0 | 0 | 0 |
| Psychiatric disorders | n (%) | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (5.6) |
| Anxiety | n (%) | 0 | 0 | 0 | 0 | 1 (14.3) | 1 (5.6) |

Source: Listing 16.2.7.1
TEAE = treatment emergent adverse event
Adverse events are coded to system organ class and preferred term using MedDRA Version 23.0.
If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count (n) column for a given System Organ Class and Preferred Term.
Any adverse event that occurred on or prior to escape event is counted in the SOC column, and after escape event is counted in the SOC to pegcetacoplan column.
Only categories (defined by Preferred Term) with >=5% TEAEs in any group are displayed along with their corresponding System Organ Class categories. Under a System Organ Class category, there may be some Preferred Term subcategories which did not meet the frequency criteria and consequently are not displayed. Thus, the sum of AEs within the displayed Preferred Term subcategories may be fewer than the AEs indicated within the corresponding System Organ Class category.
Program: t_14_3_1_11_2.sas Output: t_14_3_1_11_2.rtf Run: 2021-10-06 18:48 Database Lock Date: 2021-08-05

- Exposure-adjusted incidence of TEAEs

Exposure-adjusted incidence of TEAEs is presented in CSR, Tables 14.3.1.15.1 and 14.3.1.15.2. Exposure-adjusted incidences for TEAEs that occurred in ≥5% of subjects in any treatment group by SOC and PT during the whole study are presented in the table below.

**Table 45: Exposure-adjusted incidences for TEAEs that occurred in ≥5% of subjects in any treatment group by SOC and PT during the whole study**

| System Organ Class/ Preferred Term | Overall pegcetacoplan (N = 46) | SoC (while on SoC) (N = 18) |
|---|---|---|
| **Exposure-years** | 28.5 | 5.4 |
| **Number of subjects with at least one TEAE, n (e)** | 35 (122.7) | 12 (220.4) |
| **General disorders and administration site conditions, n (e)** | 19 (66.6) | 1 (18.4) |
| Pyrexia | 4 (14.0) | 0 |
| Injection site bruising | 2 (7.0) | 0 |
| Injection site haemorrhage | 2 (7.0) | 0 |
| Injection site swelling | 2 (7.0) | 0 |
| Peripheral swelling | 2 (7.0) | 0 |
| Vaccination site pain | 2 (7.0) | 0 |
| Fatigue | 1 (3.5) | 1 (18.4) |
| Malaise | 0 | 1 (18.4) |
| **Skin and subcutaneous tissue disorders, n (e)** | 12 (42.1) | 0 |
| Ecchymosis | 3 (10.5) | 0 |
| Erythema | 3 (10.5) | 0 |
| Rash | 2 (7.0) | 0 |
| Rash maculo-papular | 2 (7.0) | 0 |
| **Infections and infestations, n (e)** | 11 (38.6) | 5 (91.8) |
| Viral infection | 3 (10.5) | 0 |
| COVID-19 | 2 (7.0) | 0 |
| Helicobacter gastritis | 1 (3.5) | 0 |
| Oesophageal candidiasis | 1 (3.5) | 0 |
| Septic shock | 1 (3.5) | 1 (18.4) |
| Upper respiratory tract infection | 1 (3.5) | 2 (36.7) |
| Herpes virus infection | 0 | 1 (18.4) |
| Influenza | 0 | 1 (18.4) |
| Pneumocystis jirovecii pneumonia | 0 | 1 (18.4) |
| Pulmonary tuberculosis | 0 | 1 (18.4) |
| Urinary tract infection | 0 | 2 (36.7) |
| **Metabolism and nutrition disorders, n (e)** | 11 (38.6) | 3 (55.1) |
| Hypokalaemia | 6 (21.0) | 2 (36.7) |
| Hypophosphataemia | 2 (7.0) | 0 |
| Hyperuricaemia | 1 (3.5) | 1 (18.4) |
| Dehydration | 0 | 1 (18.4) |
| Metabolic acidosis | 0 | 1 (18.4) |

| | | |
|---|---|---|
| **Blood and lymphatic system disorders, n (e)** | 10 (35.0) | 3 (55.1) |
| Anaemia | 3 (10.5) | 1 (18.4) |
| Haemolysis | 3 (10.5) | 0 |
| Thrombocytopenia | 3 (10.5) | 1 (18.4) |
| Neutropenia | 2 (7.0) | 0 |
| Bone marrow failure | 1 (3.5) | 1 (18.4) |
| Febrile neutropenia | 1 (3.5) | 1 (18.4) |
| **Musculoskeletal and connective tissue disorders, n (e)** | 10 (35.0) | 1 (18.4) |
| Pain in extremity | 6 (21.0) | 0 |
| Arthralgia | 5 (17.5) | 0 |
| Musculoskeletal pain | 3 (10.5) | 0 |
| Back pain | 2 (7.0) | 0 |
| Plantar fasciitis | 0 | 1 (18.4) |
| **Gastrointestinal disorders, n (e)** | 9 (31.5) | 2 (36.7) |
| Abdominal pain | 3 (10.5) | 0 |
| Abdominal pain upper | 3 (10.5) | 1 (18.4) |
| Diarrhoea | 2 (7.0) | 0 |
| Gastritis | 2 (7.0) | 0 |
| Nausea | 2 (7.0) | 0 |
| Dyspepsia | 1 (3.5) | 1 (18.4) |
| **Respiratory, thoracic and mediastinal disorders, n (e)** | 9 (31.5) | 4 (73.5) |
| Cough | 3 (10.5) | 0 |
| Epistaxis | 3 (10.5) | 0 |
| Dyspnoea | 1 (3.5) | 1 (18.4) |
| Oropharyngeal discomfort | 1 (3.5) | 1 (18.4) |
| Oropharyngeal pain | 1 (3.5) | 0 |
| Rhinitis allergic | 1 (3.5) | 1 (18.4) |
| Rhinorrhoea | 1 (3.5) | 0 |
| Respiratory failure | 0 | 1 (18.4) |
| **Nervous system disorders, n (e)** | 8 (28.0) | 0 |
| Dizziness | 5 (17.5) | 0 |
| Headache | 4 (14.0) | 0 |
| Somnolence | 3 (10.5) | 0 |
| Aphonia | 1 (3.5) | 0 |

| | | |
|---|---|---|
| **Investigations, n (e)** | 7 (24.5) | 0 |
| Blood creatinine increased | 3 (10.5) | 0 |
| Activated partial thromboplastin time prolonged | 2 (7.0) | 0 |
| Alanine aminotransferase increased | 2 (7.0) | 0 |
| Blood creatine phosphokinase increased | 2 (7.0) | 0 |
| Gamma-glutamyltransferase increased | 2 (7.0) | 0 |
| **Renal and urinary disorders, n (e)** | 5 (17.5) | 1 (18.4) |
| Polyuria | 2 (7.0) | 0 |
| Dysuria | 1 (3.5) | 0 |
| Acute kidney injury | 0 | 1 (18.4) |
| **Injury, poisoning and procedural complications, n (e)** | 4 (14.0) | 1 (18.4) |
| Skin abrasion | 0 | 1 (18.4) |
| **Hepatobiliary disorders, n (e)** | 2 (7.0) | 0 |
| Bile duct stone | 1 (3.5) | 0 |
| **Vascular disorders, n (e)** | 2 (7.0) | 0 |
| Hypertension | 1 (3.5) | 0 |
| Hypotension | 1 (3.5) | 0 |
| **Psychiatric disorders, n (e)** | 0 | 1 (18.4) |
| Anxiety | 0 | 1 (18.4) |

Abbreviations: EY = exposure-years; MedDRA = Medical Dictionary for Regulatory Activities; SoC = standard of care; TEAE = treatment-emergent adverse event

n = number of subjects with that adverse event, e = rate per 100 events-years calculated as 100*n/EY, where EY are calculated as the sum of (last study drug exposure date - first study drug exposure date +1)/365.25 during whole period for all subjects. For subjects on SoC, duration on study will be used, as exposure years calculated as (last date on SoC - randomization date + 1)/365.25.

Adverse events are coded to System Organ Class and Preferred Term using MedDRA Version 23.0.

If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count (n) column for a given System Organ Class and Preferred Term.

Any adverse event that occurred on or prior to escape event is counted in the SoC column, and after escape event is counted in the SoC to pegcetacoplan column.

Only categories (defined by Preferred Term) with >=5% TEAEs in any group are displayed along with their corresponding System Organ Class categories. Under a System Organ Class category, there may be some Preferred Term subcategories which did not meet the frequency criteria and consequently are not displayed. Thus, the sum of AEs within the displayed Preferred Term subcategories may be fewer than the AEs indicated within the corresponding System Organ Class category.

Overall pegcetacoplan refers to subjects who have received pegcetacoplan at any point during the study.

Source: Appendix 16.2.7, Listing 16.2.7.1; Table 14.3.1.11.4.

- Severe adverse events

*Pegcetacoplan group*

- One subject in the pegcetacoplan group had 1 severe TEAE of chest pain, which was deemed possibly related to pegcetacoplan and was resolved with treatment.
- One subject in the pegcetacoplan group had 1 severe TEAE of neutropenia, which was deemed not related to pegcetacoplan and was resolved with treatment.
- One subject in the pegcetacoplan group had 4 severe TEAEs:
  - anaemia, which was deemed not related to pegcetacoplan because it occurred before the first drug administration and was resolved with treatment
  - pancytopenia, which was deemed not related to pegcetacoplan because it was diagnosed at baseline and was ongoing at the time of the patient's death
  - febrile neutropenia, which was deemed not related to pegcetacoplan and was resolved with treatment
  - Septic shock, which was deemed not related to pegcetacoplan, was not treated, and was fatal. A blood culture was positive for *Klebsiella pneumoniae* while the

subject was hospitalized for febrile neutropenia, approximately 2 weeks prior to death; however, the patient refused treatment and was discharged at their own request. The investigator was later informed that the subject developed a perianal abscess that fistulized and that the subject died at home the day after. The cause of death was reported as septic shock related to bone marrow aplasia; however, no autopsy was performed.

- One subject in the pegcetacoplan group had 2 severe TEAEs:
  - Haemolysis, which was deemed not related to pegcetacoplan, was resolved with treatment, and resulted in a dose increase.
  - Lymphopenia, which was deemed related to pegcetacoplan, was not treated, and was resolving at study completion

*SoC to pegcetacoplan group*

- One subject in the SoC to pegcetacoplan group had 2 severe TEAEs:
  - hypokalaemia, which was deemed not related to pegcetacoplan and resolved with treatment
  - anaemia, which was deemed not related to pegcetacoplan and resolved with treatment
- One subject in the SoC to pegcetacoplan group had 1 severe TEAE of anaemia, which was deemed unlikely related to pegcetacoplan and resolved with treatment
- One subject in the SoC to pegcetacoplan group had 1 severe TEAE of bile duct stone, which was deemed not related to pegcetacoplan and resolved with treatment

*SoC group*

- One subject in the SoC group had 7 severe TEAEs. The subject was in the SoC arm and never received pegcetacoplan, so all the events were assessed as not related to pegcetacoplan:
  - thrombocytopenia, which required treatment and was fatal
  - febrile neutropenia, which required treatment and was fatal
  - herpes viral infection, which required treatment and was fatal
  - urinary tract infection, which required treatment and was fatal
  - septic shock, which required treatment and was fatal
  - pulmonary tuberculosis, which required treatment and was fatal
  - respiratory failure, which required treatment and was fatal

<u>Treatment-related adverse events</u>

The table below presents a summary of the total number of TEAEs for the safety set deemed related by the investigator to the study drug.

**Table 46: Summary of the total number of TEAEs for the safety set deemed related by the investigator to the study drug**

| | RCP | Whole study |
|---|---|---|
| System Organ Class<br>Preferred Term | Overall pegcetacoplan<br>(N = 46) | Overall pegcetacoplan<br>(N = 46) |
| **Number of subjects with at least one pegcetacoplan-related TEAE, n (%)** | 13 (28.3) | 16 (34.8) |
| **General disorders and administration site conditions, n (%)** | 5 (10.9) | 5 (10.9) |
| Injection site bruising | 2 (4.3) | 2 (4.3) |
| Chest pain | 1 (2.2) | 1 (2.2) |
| Induration | 1 (2.2) | 1 (2.2) |
| Infusion site pruritus | 1 (2.2) | 1 (2.2) |
| Puncture site reaction | 1 (2.2) | 1 (2.2) |
| **Metabolism and nutrition disorders, n (%)** | 5 (10.9) | 5 (10.9) |
| Hypokalaemia | 3 (6.5) | 3 (6.5) |
| Hypophosphataemia | 1 (2.2) | 1 (2.2) |
| Vitamin D deficiency | 1 (2.2) | 1 (2.2) |
| **Skin and subcutaneous tissue disorders, n (%)** | 4 (8.7) | 4 (8.7) |
| Rash | 2 (4.3) | 2 (4.3) |
| Ecchymosis | 1 (2.2) | 1 (2.2) |
| Rash maculo-papular | 1 (2.2) | 1 (2.2) |
| **Musculoskeletal and connective tissue disorders, n (%)** | 3 (6.5) | 3 (6.5) |
| Arthralgia | 1 (2.2) | 1 (2.2) |
| Arthritis | 1 (2.2) | 1 (2.2) |
| Back pain | 1 (2.2) | 1 (2.2) |
| Myalgia | 1 (2.2) | 1 (2.2) |
| Pain in extremity | 1 (2.2) | 1 (2.2) |
| **Gastrointestinal disorders, n (%)** | 2 (4.3) | 2 (4.3) |
| Abdominal pain upper | 1 (2.2) | 1 (2.2) |
| Diarrhoea | 1 (2.2) | 1 (2.2) |
| **Investigations, n (%)** | 2 (4.3) | 3 (6.5) |
| Activated partial thromboplastin time prolonged | 1 (2.2) | 2 (4.3) |
| Alanine aminotransferase increased | 1 (2.2) | 2 (4.3) |
| Blood creatine phosphokinase increased | 1 (2.2) | 1 (2.2) |
| Blood creatinine increased | 1 (2.2) | 2 (4.3) |
| Blood phosphorus decreased | | 1 (2.2) |
| Gamma-glutamyltransferase increased | | 1 (2.2) |

| | | |
|---|---|---|
| Blood fibrinogen | | 1 (2.2) |
| **Nervous system disorders, n (%)** | 2 (4.3) | 2 (4.3) |
| Dizziness | 2 (4.3) | 2 (4.3) |
| Somnolence | 2 (4.3) | 2 (4.3) |
| **Cardiac disorders, n (%)** | 1 (2.2) | 1 (2.2) |
| Tachycardia | 1 (2.2) | 1 (2.2) |
| **Respiratory, thoracic and mediastinal disorders, n (%)** | 1 (2.2) | 1 (2.2) |
| Oropharyngeal discomfort | 1 (2.2) | 1 (2.2) |
| **Vascular disorders, n (%)** | 1 (2.2) | 1 (2.2) |
| Hypertension | 1 (2.2) | 1 (2.2) |
| **Blood and lymphatic system disorders, n (%)** | | 3 (6.5) |
| Haemolysis | | 1 (2.2) |
| Lymphopenia | | 1 (2.2) |
| Neutropenia | | 1 (2.2) |
| Thrombocytopenia | | 1 (2.2) |

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; RCP = randomized controlled period; SoC = standard of care; TEAE = treatment-emergent adverse event; n = number of subjects.
Adverse events are coded to System Organ Class and Preferred Term using MedDRA Version 23.0.
If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count (n) column for a given System Organ Class and Preferred Term.
Definitely related and possibly related adverse events are classified as drug related AEs. Adverse events with unknown relationship to study drug is counted as related.
Any adverse event that occurred on or prior to escape event is counted in the SoC column, and after escape event is counted in the SoC to pegcetacoplan column. Overall Pegcetacoplan refers to subjects who have received pegcetacoplan at any point during the study.
Source: Appendix 16.2.7, Listing 16.2.7.1; Table 14.3.1.4.1; Table 14.3.1.4.2.

Adverse events of special interest (AESIs)

Because of the mechanism of action of pegcetacoplan, route of administration, and relevance to PNH, selected TEAEs were identified and defined as follows:

- ISRs: AEs from the injection site or related to pump use that the investigator determined to be clinically relevant
- infections, including sepsis : events in the MedDRA SOC of infections and infestations
- haemolytic disorders: events in the MedDRA SMQ of haemolytic disorders thrombosis events: events in the MedDRA High Level Group Term of embolism and thrombosis
- hypersensitivity events: events in the MedDRA SMQ of hypersensitivity

The table below presents the numbers of events in the selected AE categories.

**Table 47: Treatment-Emergent Adverse Events in Special Search Categories by Study**

| | RCP | |
|---|---|---|
| AE special search category, n (%) | Overall pegcetacoplan (N = 46) | SoC (while on SoC) (N = 18) |
| Hypersensitivity | 9 (19.6) | 1 (5.6) |
| Infections | 9 (19.6) | 5 (27.8) |
| Sepsis | 0 | 0 |
| Injection site reactions | 14 (30.4) | - |
| Hemolytic disorders | 0 | 0 |
| Thrombosis | 0 | 0 |
| | Whole study | |
| AE special search category, n (%) | Overall pegcetacoplan (N = 46) | SoC (while on SoC) (N = 18) |
| Hypersensitivity | 12 (26.1) | 2 (11.1) |
| Infections | 11 (23.9) | 5 (27.8) |
| Sepsis* | 1 (2.2) | 1 (5.6) |
| Injection site reactions | 16 (34.8) | - |
| Hemolytic disorders | 3 (6.5) | 0 |
| Thrombosis | 0 | 0 |

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; RCP = randomized controlled period; SoC = standard of care.
A treatment-emergent adverse event is defined as an adverse event that starts on or after the first dose of investigational product for APL2 group, on or after randomization date for SoC group. Adverse events are coded to System Organ Class and Preferred Term using MedDRA Version 23.0.
Adverse events in special search categories includes hemolytic disorders, hypersensitivity, sepsis, infections, thrombosis.
Time to onset (day) = TEAE start date – randomization date +1. If a subject has the same AE on multiple occasions, the first presence will be included in the table.
Any adverse event that occurred on or prior to escape event is counted in the SoC column, and after escape event is counted in the SoC to pegcetacoplan column. Overall Pegcetacoplan refers to subjects who have received pegcetacoplan at any point during the study.
*Sepsis refers to 2 events of septic shock (Preferred Term) occurring during the overall study period
Source: Appendix 16.2.7, Listing 16.2.7.1; Table 14.3.1.16.1; Table 14.3.1.16.2; Table 14.3.1.5.1.1; Table 14.3.1.5.1.2.

*Injection Site Reactions*

The table below presents by SOC and PT an overall summary of the total number of subjects experiencing at least 1 ISR during the RCP and the whole study.

**Table 48: Injection Site Reaction Treatment-Emergent Adverse Events by System Organ Class and Preferred Term during the RCP and the Whole Study (Safety Set)**

| | RCP | Whole study |
|---|---|---|
| | **Overall pegcetacoplan (N = 46)** | **Overall pegcetacoplan (N = 46)** |
| **Number of subjects with at least one ISR TEAE, n (%)** | 14 (30.4) | 16 (34.8) |
| Mild | 14 (30.4) | 16 (34.8) |
| Moderate | 0 | 0 |
| Severe | 0 | 0 |
| **System Organ Class/ Preferred Term** | | |
| **General disorders and administration site conditions, n (%)** | 10 (21.7) | 11 (23.9) |
| Injection site bruising | 2 (4.3) | 2 (4.3) |
| Injection site haemorrhage | 2 (4.3) | 2 (4.3) |
| Induration | 1 (2.2) | 1 (2.2) |
| Inflammation | 1 (2.2) | 1 (2.2) |
| Injection site rash | 1 (2.2) | 1 (2.2) |
| Peripheral swelling | 1 (2.2) | 1 (2.2) |
| Puncture site reaction | 1 (2.2) | 1 (2.2) |
| Vaccination site reaction | 1 (2.2) | 1 (2.2) |
| Application site reaction | 0 | 1 (2.2) |
| **Skin and subcutaneous tissue disorders, n (%)** | 4 (8.7) | 4 (8.7) |
| Ecchymosis | 2 (4.3) | 2 (4.3) |
| Erythema | 2 (4.3) | 3 (6.5) |
| **Vascular disorders, n (%)** | 1 (2.2) | 1 (2.2) |
| Haematoma | 1 (2.2) | 1 (2.2) |
| **Musculoskeletal and connective tissue disorders, n (%)** | 0 | 2 (4.3) |
| Pain in extremity | 0 | 2 (4.3) |

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; RCP = randomized controlled period; SoC = standard of care; TEAE = treatment-emergent adverse event; n = number of subjects.
Adverse events are coded to System Organ Class and Preferred Term using MedDRA Version 23.0.
If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count (n) column for a given System Organ Class and Preferred Term.
Any adverse event that occurred on or prior to escape event is counted in the SoC column, and after escape event is counted in the SoC to pegcetacoplan column.
Overall Pegcetacoplan refers to subjects who have received pegcetacoplan at any point during the study.
Source: Appendix 16.2.7, Listing 16.2.7.1; Table 14.3.1.5.1.1; Table 14.3.1.5.1.2; Table 14.3.1.5.1.3; Table 14.3.1.5.1.4.

*Infections*

The table below present treatment-emergent infections by PT for the safety set during the whole study.

**Table 49: Treatment-emergent infections by PT for the safety set during the whole study**

| | Overall pegcetacoplan (N = 46) | SoC (while on SoC) (N = 18) |
|---|---|---|
| **Number of subjects with at least one infections and infestations TEAE, n (%)** | 11 (23.9) | 5 (27.8) |
| Mild | 6 (13.0) | 3 (16.7) |
| Moderate | 4 (8.7) | 1 (5.6) |
| Severe | 1 (2.2) | 1 (5.6) |
| **Preferred Term, n (%)** | | |
| Viral infection | 3 (6.5) | 0 |
| COVID-19 | 2 (4.3) | 0 |
| Acne pustular | 1 (2.2) | 0 |
| Anal abscess | 1 (2.2) | 0 |
| COVID-19 pneumonia | 1 (2.2) | 0 |
| Cellulitis | 1 (2.2) | 0 |
| Gastroenteritis | 1 (2.2) | 0 |
| Helicobacter gastritis | 1 (2.2) | 0 |
| Hordeolum | 1 (2.2) | 0 |
| Nasopharyngitis | 1 (2.2) | 0 |
| Oesophageal candidiasis | 1 (2.2) | 0 |
| Pharyngitis | 1 (2.2) | 0 |
| Septic shock | 1 (2.2) | 1 (5.6) |
| Tuberculosis | 1 (2.2) | 0 |
| Upper respiratory tract infection | 1 (2.2) | 2 (11.1) |
| Urinary tract infection enterococcal | 1 (2.2) | 0 |
| Vaginal infection | 1 (2.2) | 0 |
| Herpes virus infection | 0 | 1 (5.6) |
| Influenza | 0 | 1 (5.6) |
| Pneumocystis jirovecii pneumonia | 0 | 1 (5.6) |
| Pulmonary tuberculosis | 0 | 1 (5.6) |
| Urinary tract infection | 0 | 2 (11.1) |

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; SoC =standard of care; TEAE = treatment-emergent adverse event.
Adverse events are coded to System Organ Class and Preferred Term using MedDRA Version 23.0.
If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count (n) column for a given System Organ Class and Preferred Term.
Any adverse event that occurred on or prior to escape event is counted in the SoC column, and after escape event is counted in the SoC to pegcetacoplan column. Overall Pegcetacoplan refers to subjects who have received pegcetacoplan at any point during the study.
Source: Appendix 16.2.7, Listing 16.2.7.1; Table 14.3.1.12.2; Table 14.3.1.3.2.

*Haemolysis disorders and thrombosis events*

There were no reported thrombosis events and no haemolytic disorders were reported during the RCP.

During the whole study, three haemolytic disorders were reported during the post-RCP period.

- In the pegcetacoplan group, 2 subjects (5.7%) had haemolytic disorders:
    - 1 moderate event of haemolysis deemed not related to pegcetacoplan, which resulted in a dose increase
    - 1 severe event of breakthrough haemolysis deemed not related to pegcetacoplan, which resulted in a dose increase. See Section 14.3.3 for the narrative.
- In the SoC to pegcetacoplan group, 1 subject (9.1%) had a moderate event of haemolysis, which resulted in a dose increase.

*Hypersensitivity*

The table below present TEAEs in the SMQ of hypersensitivity for the safety set during the whole study.

**Table 50: Treatment-Emergent Hypersensitivity Events by Preferred Term During the Whole Study (Safety Set)**

| | Overall pegcetacoplan (N = 46) | SoC (while on SoC) (N = 18) |
|---|---|---|
| **Number of subjects with at least one hypersensitivity TEAE, n (%)** | 12 (26.1) | 2 (11.1) |
| Mild | 11 (23.9) | 1 (5.6) |
| Moderate | 1 (2.2) | 0 |
| Severe | 0 | 1 (5.6) |
| **Hypersensitivity, n (%)** | | |
| Erythema | 3 (6.5) | 0 |
| Rash | 2 (4.3) | 0 |
| Allergic cough | 1 (2.2) | 0 |
| Dermatitis | 1 (2.2) | 0 |
| Dermatitis contact | 1 (2.2) | 0 |
| Eyelid oedema | 1 (2.2) | 0 |
| Injection site rash | 1 (2.2) | 0 |
| Rash maculo-papular | 2 (4.3) | 0 |
| Rhinitis allergic | 1 (2.2) | 1 (5.6) |
| Respiratory failure | 0 | 1 (5.6) |
| Pruritus | 1 (2.2) | 0 |

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; SoC = standard of care; TEAE = treatment-emergent adverse event.
A treatment-emergent adverse event is defined as an adverse event that starts on or after the first dose of investigational product for APL2 group, on or after randomization date for SoC group.
Adverse events are coded to System Organ Class and Preferred Term using MedDRA Version 23.0.
Time to onset (day) = TEAE start date – randomization date +1. If a subject has the same AE on multiple occasions, the first presentation will be included in the table.
Any adverse event that occurred on or prior to escape event is counted in the SoC column, and after escape event is counted in the SoC to pegcetacoplan column. Overall Pegcetacoplan refers to subjects who have received pegcetacoplan at any point during the study.
Source: Appendix 16.2.7, Listing 16.2.7.1; Table 14.3.1.16.2; Table 14.3.1.16.5.

## *Serious adverse event/deaths/other significant events*

Serious adverse events

**Table 51: Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term during the Whole Study (Safety Set)**

| System Organ Class/ Preferred Term | Overall pegcetacoplan (N = 46) | SoC (while on SoC) (N = 18) |
|---|---|---|
| **Number of subjects with at least one serious TEAE, n (%)** | 6 (13.0) | 3 (16.7) |
| **Blood and lymphatic system disorders, n (%)** | 4 (8.7) | 2 (11.1) |
| Anaemia | 1 (2.2) | 0 |
| Febrile neutropenia | 1 (2.2) | 1 (5.6) |
| Haemolysis | 1 (2.2) | 0 |
| Neutropenia | 1 (2.2) | 0 |
| Pancytopenia | 1 (2.2) | 0 |
| Bone marrow failure | 0 | 1 (5.6) |
| Thrombocytopenia | 0 | 1 (5.6) |
| **Congenital, familial and genetic disorders, n (%)** | 1 (2.2) | 0 |
| Dermoid cyst | 1 (2.2) | 0 |
| **Hepatobiliary disorders, n (%)** | 1 (2.2) | 0 |
| Bile duct stone | 1 (2.2) | 0 |
| **Infections and infestations** | 1 (2.2) | 1 (5.6) |
| Septic shock | 1 (2.2) | 1 (5.6) |
| Herpes virus infection | 0 | 1 (5.6) |
| Pneumocystis jirovecii pneumonia | 0 | 1 (5.6) |
| Pulmonary tuberculosis | 0 | 1 (5.6) |
| Urinary tract infection | 0 | 1 (5.6) |
| **Metabolism and nutrition disorders, n (%)** | 0 | 1 (5.6) |
| Metabolic acidosis | 0 | 1 (5.6) |
| **Respiratory, thoracic and mediastinal disorders, n (%)** | 0 | 1 (5.6) |
| Respiratory failure | 0 | 1 (5.6) |

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SoC = standard of care; TEAE = treatment-emergent adverse event; n = number of subjects.
Adverse events are coded to System Organ Class and Preferred Term using MedDRA Version 23.0.
If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count (n) column for a given System Organ Class and Preferred Term.
Any adverse event that occurred on or prior to escape event is counted in the SoC column, and after escape event is counted in the SoC to pegcetacoplan column. Overall Pegcetacoplan refers to subjects who have received pegcetacoplan at any point during the study.
Source: Appendix 16.2.7, Listing 16.2.7.2; Table 14.3.1.6.2.

## *Laboratory findings*

Haematology

Observed and change from baseline values for haematology parameters during whole study for the safety set by analysis visit through Week 62 and by treatment group were presented in the CSR. Clinically relevant haematology parameters were selected based on the mechanisms of action of pegcetacoplan and relevance to PNH: basophils, eosinophils, erythrocytes, leukocytes, lymphocytes, monocytes, neutrophils, platelets, haematocrit, Hb, and reticulocytes.

Clinical haematology test values were potentially clinically significant (PCS) if they were low and met criteria listed in the table below.

**Table 52: Criteria for Potentially Clinically Significant Low Hematology Test Results**

| Hematology parameter | Mild | Moderate | Severe |
|---|---|---|---|
| Hb concentration (g/dL) | 10-12 | 7-10 | <7 |
| Neutrophil count (cells × $10^9$/L) | 1-1.5 | 0.5-1.0 | <0.5 |
| Platelet count (cells × $10^9$/L) | 100-150 | 50-100 | <50 |

Source: Appendix 16.1.9, SAP, Table 2.

Chemistry

Observed and change from baseline values for chemistry parameters during whole study for the safety set by analysis visit through Week 62 and by treatment group were presented in the CSR. Clinically relevant chemistry parameters were selected based on the mechanisms of action of pegcetacoplan and relevance to PNH: liver enzymes (ALT, AST, ALP), bilirubin, and LDH concentrations.

Coagulation

One subject /pegcetacoplan had a clinically significant prothrombin time of 36.4 seconds during the Week 8 visit. This subject's prothrombin time was not clinically significant at any other visits.

Urinalysis

One subject /pegcetacoplan had a TEAE of haemoglobinuria during the whole study (from Day 284 through Day 286). This event was rated moderate in severity and deemed not related to study drug or infusion process.

Pregnancy tests

During the screening period, a serum pregnancy test was performed for WOCBP, and follicle-stimulating hormone measurement was performed for postmenopausal females.

Urine pregnancy tests were performed at each visit for WOCBP. There were no positive test results in the study.

- Physical examination

Two subjects in the pegcetacoplan group each had a TEAE of oedema: one subject had leg oedema deemed moderate, while the other subject had bilateral palpebral oedema deemed mild. The oedema events in both subjects were determined to be not related to pegcetacoplan or the infusion procedure.

Vital signs, physical findings and other observation related to safety

- Vital signs

Four subjects (8.7%) each had a single TEAE related to vital sign abnormalities. These 4 subjects all had events of pyrexia:

  - One TEAE of pyrexia was assessed as moderate and not related to pegcetacoplan by the investigator.
  - Three were assessed as mild by the investigator:
    - Two were determined to be not related to pegcetacoplan or the infusion procedure.

- One was determined to be unlikely related to pegcetacoplan and not related to the infusion procedure.

- ECG

A summary of subjects with post-baseline ECG results by analysis visit during whole study that were considered PCS according to the criteria is presented in the table below.

**Table 53: PCS ECG Criteria**

| Parameter | Criteria |
|---|---|
| Heart rate | At least one value ≥100 bpm and one value ≤50 bpm |
| PR interval | ≥200 ms |
| QT interval | ≥480 ms |
| QRS interval | ≥120 ms |
| QTcB, QTcF | ≥480 and <500 ms<br>≥500 ms |
| QT, QTcF increase from baseline | ≥30 ms and <60 ms<br>≥60 ms |

Abbreviation: bpm = beats per minute, ECG = electrocardiogram, PCS = potentially clinically significant, QTcB = QT interval corrected for heart rate using Bazett's formula, QTcF = QT interval corrected for heart rate using Fridericia's formula.
Source: Appendix 16.1.9, SAP.

PCS ECG results occurred each ECG assessment week; the highest number of PCS results for a single parameter occurred during Week 20, when 10 subjects each had a QT increase from baseline ≥30 ms and <60 ms.

Two subjects in the pegcetacoplan group had cardiac AEs during the study:

- One subject had 2 events of bradycardia that were both mild, did not require treatment, were resolved spontaneously, and were deemed not related to pegcetacoplan or the infusion procedure. The subject's ECGs were interpreted as abnormal at baseline and throughout the study. This subject had PR intervals d, did at Weeks 26 and 50: 207.5 ms and 210.0 ms, respectively.
- One subject had 1 event of tachycardia. It was deemed mild, did not require treatment, was resolved spontaneously on the same day it occurred, and was assessed as possibly related to pegcetacoplan but not related to the infusion procedure. This event was reported 3 days before the subject's Week 12 visit. At Week 12, the subject's QT interval increase from baseline averaged 32.2 ms. The investigator's interpretation of the ECG at Week 12 was normal.

- Immunogenicity

Of the 46 subjects exposed to pegcetacoplan, 1 (2.2%) had a positive anti-pegcetacoplan peptide antibody response. One subject tested positive for anti-pegcetacoplan peptide antibodies on Day 1 before dosing. The titer was 1:<10. This subject received only one dose of pegcetacoplan and then was lost to follow-up. No other subjects were tested positive for anti–pegcetacoplan peptide antibodies at Day 1 before dosing or at any other visits in the study.

Of the 46 subjects who received at least 1 dose of pegcetacoplan, 38 tested positive for anti-PEG antibodies. Of the 38, 7 developed a treatment-emergent response and 5 developed a treatment-boosted response. In both cases, subjects who received only SoC treatment during the study were included: 1 subject developed a treatment-emergent anti-PEG response, and 3 subjects developed a treatment-boosted anti-PEG response.

### *Post marketing experience*

On 14 May 2021, pegcetacoplan was approved as Empaveli in the United States for the treatment of adult patients with PNH. This represented the first regulatory approval worldwide. As of 13 November 2022, an estimated 294 patients have received commercial pegcetacoplan and have had approximately 209.98 patient-years of cumulative exposure since launch (Periodic Safety Update Report #2, 9 Jan 2023, interval covered: 14 May 2022 to 13 Nov 2022). The estimated patient-years can be calculated from the number of dispensed vials and assuming 2 vials/week per patient (ie, 1 vial every 3.5 days or daily dose 0.286 vials/day).

Overall, the review of cases received from postmarketing sources did not reveal any new safety issue (Periodic Safety Update Report #1 and #2). The favorable safety profile of pegcetacoplan remains unchanged.

## Update of the Product information

To update the Section 4.8 of the SmPC, the previously applied determination approach remains unchanged. The addition of data from Study APL2-308 resulted in the following changes in ADRs:

- Addition of 4 new PTs in the SOC of infections and infestations: *tuberculosis*, *esophageal candidiasis*, coronavirus disease 2019 (*COVID-19*), *COVID-19 pneumonia*, and *anal abscess*.
- *Vaginal infection* is introduced as a new grouped term that includes the PTs vulvovaginal mycotic infection (previously included) and vaginal infection (new).
- *Eye infection* is also a new grouped term that includes the PTs ophthalmic herpes zoster and hordeolum (both previously included).

Based on the updated data, however, the following PTs would be presented in a lower frequency category: urinary tract infection, back pain, injection site bruising, and injection site pain. For these PTs, the Applicant has taken a conservative approach and these PTs will remain in the higher frequency category. The following PTs currently included in the adverse reaction table are now reported at <5%: hypertension, dyspnea, nasal congestion, muscle spasms, acute kidney injury, chromaturia and bilirubin increase; however, the Applicant proposes, conservatively, that they remain listed in the adverse reaction table.

Of note, for Study APL-CP0514, 6 subjects from Cohort 4 contribute to the dataset supporting the adverse reaction table. Due to the design of this study, subjects could participate in more than 1 cohort, and when preparing data outputs for the currently approved SmPC, AEs occurring outside of Cohort 4 were erroneously included. This has now been corrected, and the newly prepared outputs show that *anxiety* was not reported at ≥5% but its reporting frequency was 4.5%. Additionally, *nausea* was not reported at ≥10% but its reporting frequency was 9.1%, and therefore, it is proposed to change the frequency category for nausea from "Very common" to "Common."

Finally, with the addition of data from Study APL2-308, the PT of *anemia* now has a reporting frequency of 5.1%. However, based on these reports of anemia, these are likely secondary to the underlying disease of PNH and not an adverse reaction of pegcetacoplan. Additionally, the PT of *contusion* is not included in the adverse reaction table despite its reported frequency of greater than 5%.

Of note, the following safety-related sections of the product information remain unchanged: contraindications; special warnings and precautions; interactions; fertility, pregnancy, lactation; ability to drive and use machinery; and overdose.

## 2.5.1. Discussion on clinical safety

The summary of safety profile of pegcetacoplan is **updated** with the data from completed study APL2-308 in *complement inhibitor naïve patients*, ongoing LTE study APL2-307 and ongoing paediatric study APL2-PNH-209. **Primary safety data** are available from following clinical studies: APL2-302, APL2-308, APL2-CP-PNH-204, APL2-202, APL-CP0514. **Additional safety data** are available from ongoing studies APL2-307 and APL2-PNH-209. For the ongoing study in PNH, APL2-307, safety data (SAEs, related SAEs, deaths, and discontinuations due to AEs) are presented for completeness. There were no SAEs or deaths reported for Study APL2-PNH-209.

Studies APL2-302 and APL2-308 are pivotal, phase 3 studies. The Applicant did not integrate the data from the two Phase 3 clinical studies, APL2-302 and APL2-308, because of differences in study design and duration of treatment between the two studies, which is in accordance with the ICH M4E (R2) guidance. **Summary tabulations** presenting TEAEs and SAEs from studies APL2-308, APL2-302, APL2-202, APL2-CP-PNH-204 and APL-CP0514 are submitted. They are supporting SmPC section 4.8 proposed changes.

In PNH studies, through 13 November 2022 (i.e. the PSUR cut-off date), 170 subjects with PNH have been **exposed** to systemic pegcetacoplan for 409.3 person years; this includes 121 subjects exposed for >2 years.

**Study APL2-308** safety set is limited in terms of number of participants (35 participants received pegcetacoplan, additional 11 participants escaped from SoC arm to pegcetacoplan) that can be acceptable in the orphan setting, and in terms of duration (26-week). Comparison to the standard of care (excluding complement inhibitors) is not possible as there was basically no standard of care, by EU standards, utilised. The present assessment of the safety is based on a comparison with the safety profile in patients that were treated with C5 inhibitor.

Of note, no white race participants were enrolled. However, it seems that the ethnicity covariate was not statistically significant for the pharmacokinetics. Overall, the study APL2-308 participants (complement inhibitor naïve) were younger and healthier at the baseline compared to study APL2-302 participants (prior complement inhibitor treatment).

Different TEAE definitions were used in study APL2-308 compared to other studies. It is questionable whether AEs from different studies can be compared and combined (to ADRs) due to different definitions. The Applicant was requested to justify the study APL2-308 TEAE definition, and explain why the definition of TEAEs differed in the study APL2-308 in comparison to studies APL2-302, APL2-202, APL2-CP-PNH-204 and APL-CP0514, and how different definitions impacted interpretation of the safety data. The exposure-adjusted analysis was used to support comparison between studies APL2-302 and APL2-308, which can be acceptable. As Study APL2-308 participants, which continued active study treatment, were rolled over to the extension Study APL2-307 and did not reach 8 weeks follow-up period, no issue with regards to the interpretation of safety data is identified.

In study APL2-308, 76% (N=46) of pegcetacoplan treated participants had any TEAEs and experienced 264 events in total. 13% (N=6) were SAEs, with one TEAE (2.2%) leading to death. 35% were related to pegcetacoplan, none of which was assessed as SAE by the investigator. Roughly, Pegcetacoplan safety data from study APL2-308 and APL2-302 were roughly comparable in terms of TEAE overview items.

**Most common TEAEs** in study APL2-308 expressed by the exposure-adjusted rates were: hypokalaemia (21%), pain in extremity (21%), arthralgia (17.5%), dizziness (17.5%), pyrexia (14%), and headache (14%). **Pegcetacoplan-related AEs** are presented. Generally, pegcetacoplan-related

AEs in study APL2-308 were observed in 1-3 participants bearing in mind that there were only 16 participant with at least one pegcetacoplan-related AE.

In study APL2-308, six subjects in pegcetacoplan experienced **SAE** (with multiple events recorded). The exposure-adjusted rate of SAEs per 100 subject-years was 21.0 in the pegcetacoplan group. None of SAEs was considered related to pegcetacoplan by the investigator.

One **death** due to septic shock related to bone marrow aplasia occurred in the study APL2-308 in pegcetacoplan group. It was assessed as not related to pegcetacoplan by the investigator. There were five deaths in the completed PNH studies, none of which was deemed related to pegcetacoplan by the investigator.

Injection site reactions (ISRs), infections, haemolytic disorders, thrombosis, hypersensitivity were outlined as **adverse events of special interest**, which is in accordance to in the initial application identified AESIs. In Study APL2-308, 16 subjects (34.8%) had an **injection site reaction**. Few subjects (3; 6.5%) required concomitant medication for symptom management. Similar frequencies of ISRs were observed in study APL2-302. In the overall pegcetacoplan group, 11 subjects (23.9%) had **infections**. All infection TEAEs except one were mild or moderate in severity (refer to the information on the event of death), and were assessed by the investigator as not related to pegcetacoplan. There was no pattern observed in types of infections. There were three moderate to severe events of **haemolytic disorders** in pegcetacoplan group observed, that led to the increase of dose. All were assessed by the investigator as not related to pegcetacoplan. No TEAEs of **thrombosis** were reported during Study APL2-308. In the overall pegcetacoplan group, 12 subjects (26.1%) had events in the SMQ of **hypersensitivity**, with most common events in SMQ being erythema (6.5%), rash (4.3%), rash maculo-papular (4.3%). Injection site rash and one unspecified rash were assessed as pegcetacoplan-related by the investigator. Of note, one SAE of hypersensitivity was reported in Study APL2-CP-PNH-204.

There were no **discontinuations** from pegcetacoplan treatment or from the study due to AEs in Study APL2-308.

**Immunogenicity** data from study APL2-308 are not worrisome. There was a low incidence of ADA positive and NAb positive samples (1 for each category of 237 samples analysed from 46 participants) with low titers for positive samples, which is expected for complement inhibitor naïve participants and is in line with finding from other studies.

Of the 46 subjects who received at least 1 dose of pegcetacoplan, 38 tested positive for anti-PEG antibodies. Of the 38, 7 developed a treatment-emergent response, and 5 developed a treatment-boosted response. There was no clear association between anti-PEG Ab responses and hypersensitivity reactions that did resolve without dose modification or treatment discontinuation. Listing of immunogenicity as an important potential risk in the list of safety concerns is adequate.

**Post-marketing data** and **laboratory findings** revealed no new safety issue.

**Overall**, in both pivotal studies (APL2-302 and APL2-308) most pegcetacoplan treated participants experienced at least one TEAE, most of which were deemed pegcetacoplan-unrelated by the investigator. AEs were relatively comparable in two pivotal studies. There were also AEs unique to each study, but were low in frequencies. Most of AESIs were broadly comparable between pivotal studies. Safety data from supportive studies were generally consistent.

**Changes to the approved Product information** have been thoroughly justified and are agreed (SmPC, section 4.8.)

Median duration of exposure to pegcetacoplan in the experimental arm was 183.0 days compared to 133.0 days in subjects who switched to pegcetacoplan. Considering the mean duration of exposure between the two subgroups, the average difference in treatment duration of 55.7 days, which questioned the comparability of data. Complementary data showed that this difference had a limited impact on safety data.

Pegcetacoplan was to be administered at a dosage of 1080 mg twice weekly. The dosage could be adjusted to pegcetacoplan 1080 mg every 3 days, as recommended in Aspaveli PI. Two subjects (1 in the pegcetacoplan group and 1 in the SoC to pegcetacoplan group) had such dose adjustments. None of the presented AEs associated to alarming efficacy nor safety outcomes.

Also, a case of temporary interruption has been reported and has been discussed in response to RSI. One subject had two pegcetacoplan dose interruptions (5 and 2 minutes, respectively) as the syringe needed to be repositioned. In both cases, the subject received the correction volume of infusion without any impact on the efficacy and safety outcomes.

Skin and subcutaneous tissue disorders were also common in this group (26.1% vs. 0%) with cases of Ecchymosis (3 subjects, 6.5%), Erythema (2 subjects, 4.3%) and Rash (2 subjects, 4.3%). The absence of such events in the highly transfused SoC group was surprising. But as patients were allowed to receive transfusions as part of their PNH management, the absence of such AEs could be explained by the fact that symptoms present at study start that do not worsen were not considered as AEs.

The rate of subjects with 'Infections and infestations' was lower in the overall pegcetacoplan group (17.4% vs. 27.8%): 2 subjects presented unspecified viral infections (4.3%) and another one had upper respiratory tract infection (2.2%). The other infectious events were not specified. In the SoC group, 5 subjects (27.8%) presented an infection, urinary tract infection being the most common (2 subjects, 11.1%) followed by Influenza, *Pneumocystis jirovecii* pneumonia and upper respiratory tract infection (1 subject each, 5.6%).

Four subjects of the overall pegcetacoplan group presented TEAEs under the SOC 'Injury, poisoning and procedural complications' that have been specified in response to RSI. All events reported were mild or moderate and resolved without any change in pegcetacoplan dose.

## 2.5.2. Conclusions on clinical safety

The summary of safety profile of pegcetacoplan is updated with the data from completed study APL2-308 in complement inhibitor naïve patients. Study APL2-308 safety database is limited in terms of size and duration. Comparison is done with the safety data from study APL2-302 which included patients that were treated with C5 inhibitor and known safety profile of pegcetacoplan is done. No new safety signals arose and pegcetacoplan safety profile remains manageable. Section 4.8 of the SmPC has been updated to reflect the study information.

## 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## 2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version 2.0 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

## Safety concerns

**Table 54: Summary of safety concerns**

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

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

## Pharmacovigilance plan

**Table 55: Ongoing and planned additional pharmacovigilance activities**

| **Study**<br>**Status** | **Summary of objectives** | **Safety concerns addressed** | **Milestones** | **Due dates** |
|---|---|---|---|---|
| **Category 1 –** Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| **Category 2 –** Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances | | | | |
| N/A | N/A | N/A | N/A | N/A |
| **Category 3 -** Required additional pharmacovigilance activities *(by the competent authority)* | | | | |

| Study<br>Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| PASS using registry data for pegcetacoplan<br>Sobi.PEGCET-301<br>Planned | To evaluate the occurrence of serious infections in patients with PNH treated with pegcetacoplan | • Serious infections<br>• Serious hypersensitivity reactions<br>• IVH after drug discontinuation<br>• Immunogenicity<br>• Malignancies and hematologic abnormalities<br>• Potential long-term of effects of PEG accumulation<br>• Use in patients with BMF<br>• Long-term safety (>1 year) | Submission of final protocol:<br>Start of data collection:<br>End of data collection:<br>Interim study reports:<br>Progress report:<br>Final study report: | Within 6 months of marketing authorization<br>Q3/Q4 2022<br>Q4 2027<br>Annually throughout the PASS<br>Twice per year until the end of the study<br><1 year after last patient, last visit |
| PASS using registry data for pegcetacoplan<br>Sobi.PEGCET-302<br>Planned | To evaluate data on pregnancy outcomes | • Missing information: Use in pregnant women | Submission of final protocol:<br>Start of data collection:<br>End of data collection:<br>Interim study reports:<br>Final study report: | Within 6 months of marketing authorization<br>Q3/Q4 2022<br>Q4 2032<br>Annually throughout the PASS<br><1 year after the outcome of the last pregnancy observed is obtained |
| Study APL2-307<br>Ongoing | To evaluate the long-term safety and efficacy of pegcetacoplan in subjects with PNH | • Serious infections<br>• Serious hypersensitivity reactions<br>• IVH after drug discontinuation<br>• Immunogenicity<br>• Malignancies and hematologic abnormalities<br>• Potential long-term | Final report: | Q1 2026 |

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| | | effects of PEG accumulation<br>• Long-term safety (>1 year) | | |

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

## *Risk minimisation measures*

**Table 56: Summary table of pharmacovigilance activities and risk minimization activities by safety concern**

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| **Important potential risks** | | |
| Serious infections | Routine risk minimization measures:<br>• SmPC Section 4.3, Section 4.4, and Section 4.8<br>• Package Leaflet<br>• Section 2, Section 3, and Section 4<br>Additional risk minimization measures:<br>• Guide for healthcare professionals<br>• Patient card<br>• Patient/carer guide<br>• Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines)<br>• System for controlled distribution | Additional pharmacovigilance activities:<br>1. Collection of safety data from long-term extension Study APL2-307<br>2. PASS (Study Sobi.PEGCET-301) using registry data for pegcetacoplan |
| Serious hypersensitivity reactions | Routine risk minimization measures:<br>• SmPC Section 4.3 and Section 4.4<br>• Package Leaflet Section 2<br>Additional risk minimization measures:<br>• Guide for healthcare professionals<br>• Patient/carer guide | Additional pharmacovigilance activities:<br>1. Collection of safety data from long-term extension Study APL2-307<br>2. PASS (Study Sobi.PEGCET-301) using registry data for pegcetacoplan |
| IVH after drug discontinuation | Routine risk minimization measures:<br>• SmPC Section 4.2 and Section 4.4<br>• Package Leaflet Section 2, Section 3, and Section 4<br>Additional risk minimization measures:<br>• Guide for healthcare professionals | Additional pharmacovigilance activities:<br>1. Collection of safety data from long-term extension Study APL2-307<br>2. PASS (Study Sobi.PEGCET-301) using registry data for pegcetacoplan |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | • Patient/carer guide | |
| Immunogenicity | Routine risk minimization measures:<br>• SmPC Section 4.8<br>Additional risk minimization measures:<br>• None | Additional pharmacovigilance activities:<br>1. Collection of safety data from long-term extension Study APL2-307<br>2. PASS (Study Sobi.PEGCET-301) using registry data for pegcetacoplan |
| Malignancies and hematologic abnormalities | Routine risk minimization measures:<br>• None.<br>Additional risk minimization measures:<br>• None | Additional pharmacovigilance activities:<br>1. Collection of safety data from long-term extension Study APL2-307<br>2. PASS (Study Sobi.PEGCET-301) using registry data for pegcetacoplan |
| Potential long-term effects of PEG accumulation | Routine risk minimization measures:<br>• SmPC Section 4.4 and Section 5.3<br>Additional risk minimization measures:<br>• Guide for healthcare professionals | Additional pharmacovigilance activities:<br>1. Collection of safety data from long-term extension Study APL2-307<br>2. PASS (Study Sobi.PEGCET-301) using registry data for pegcetacoplan |
| **Missing information** | | |
| Use in patients with BMF | Routine risk minimization measures:<br>• None<br>Additional risk minimization measures:<br>• None | Additional pharmacovigilance activities:<br>1. PASS (Study Sobi.PEGCET-301) using registry data for pegcetacoplan |
| Use in pregnant women | Routine risk minimization measures:<br>• SmPC Section 4.4, Section 4.6 and Section 5.3<br>• Package Leaflet Section 2<br>Additional risk minimization measures:<br>• None | Additional pharmacovigilance activities:<br>1. PASS (Study Sobi.PEGCET-302) using registry data for pegcetacoplan |
| Long-term safety (>1 year) | Routine risk minimization measures:<br>• SmPC Section 4.2, Section 4.4, Section 4.6, Section 4.8, and Section 5.2<br>• Package Leaflet Section 4<br>Additional risk minimization measures:<br>• None | Additional pharmacovigilance activities:<br>1. Collection of safety data from long-term extension Study APL2-307<br>2. PASS (Study Sobi.PEGCET-301) using registry data for pegcetacoplan |

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

## *2.7. Update of the Product information*

As a result of this variation, sections 4.1, 4.8, 5.1, 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section

above.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the proposed changes to the Package Leaflet are limited to the sections "What is ASPAVELI used for", "Dose", and "Possible side effects". The format and overall visual design of the package leaflet remains unchanged.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The claimed indication for Aspaveli is for monotherapy treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

### 3.1.2. Available therapies and unmet medical need

PNH is an acquired, rare, clonal and potentially life-threatening non-malignant hematologic disease characterized by complement-mediated red blood cell (RBC) haemolysis, with or without haemoglobinuria, an increased susceptibility to thrombotic episodes, and/or some degree of bone marrow dysfunction. Although there have been reports of spontaneous remission, the course of the disease is generally chronically progressive.

Historically, management of PNH was limited to the use of supportive treatments, such as blood transfusions and anticoagulation therapy. Other supportive treatments are now part of the therapeutic arsenal to reduce other symptoms, stimulate haematopoiesis and limit complications.

Allogeneic bone marrow transplantation (BMTx) and complement inhibitor therapies (Soliris and Ultomiris, two C5 inhibitors approved in 2007 and 2019, respectively) are the only effective therapies for the treatment of adult patients with PNH. But BMTx is associated with substantial morbidity and mortality and a non-negligible proportion of patients still have underlying haemolysis after C5 inhibition, which may lead to clinically significant sequalae.

With the advent of new therapies, PNH treatment is currently moving from C5 inhibitors to proximal inhibitors (Fattizzo 2023; Panse 2023).

### 3.1.3. Main clinical studies

The main evidence for efficacy and safety is based on APL2 study (N=53), a Phase 3, randomized, multicenter, open-label and controlled study to evaluate the efficacy and safety of pegcetacoplan in adult subjects with PNH who are complement inhibitor-naïve or have not recently received complement therapy.

A total of 53 patients were randomized, including 35 subjects in the pegcetacoplan group and 18 in the SoC group (complement inhibitor excluded). The treatments arms were overall balanced in terms of age, sex, BMI and baseline characteristics: the subject population was mostly under 65 years with a mean age of 44.5 ± 14.00 years and an average BMI of 23.68 ± 3.980 kg/m². Time since PNH diagnosis (5 years) and other baseline disease characteristics were similar between arms.

Patients included were mostly Asian (65.7% in the treatment group vs. 88.9% in the control group) or American Indian/Alaska Native (25.7% and 11.1%) but the possibility for extrapolation was shown in terms of race. As of 5 August 2021, the rate of protocol deviations was overall similar between pegcetacoplan and SoC groups (91.4% and 94.4% respectively). The proportion of subjects with major protocol deviations was also comparable between groups (37.1% vs. 33.3% in the SoC group) and the impact of noncompliance to vaccination requirements and drug administration was limited.

## *3.2. Favourable effects*

The proportion of subjects with Hb stabilization (avoidance of a >1 g/dL decrease at Week 26) was 85.7% in the pegcetacoplan group adjusted difference: 0.7311 [95% CI 0.5720-0.8902]; p-value <0.0001) compared to 0% the SoC group. This was further supported by an *ad hoc* analysis: Hb stabilization, defined as avoidance of a >2 g/dL decrease, concerned 88.6% of subjects from the experimental arm (adjusted difference: 0.7505 [95% CI, 0.5969-0.9041]).

Change in LDH concentration from baseline to Week 26 was the second efficacy co-primary endpoint. The difference between the pegcetacoplan and SoC groups was –1470.38 (95% CI, –2113.44 to –827.32) with a p-value of <0.0001,

As part of secondary endpoints, the proportion of subjects with Hb response (≥ 1 g/dL increase Hb from baseline to Week 26) was 71.4% in the pegcetacoplan group compared to 5.6% in the control group (adjusted difference: 0.5411 [95% CI, 0.3390-0.7431]; p-value <0.0001).

Consistent results were observed regarding changes from baseline in ARC (adjusted difference: -103.82 [95% CI: –158.90 to –48.74]; p-value <0.0002) and in Hb (adjusted difference: 2.67 g/dL [95% CI, 0.99-4.35]; p-value <0.0019).

Regarding the transfusion need, 11.4% of subjects from the pegcetacoplan group received a transfusion or had a decrease of >2 g/dL from baseline compared 100% in the SoC group (adjusted difference: –0.7505 [95% CI,–0.9041 to –0.5969]). Transfusion avoidance was higher in the treatment group with 32 subjects (91.4%) avoiding transfusion compared to 1 subject (5.6%) in the SoC group (adjusted difference: 0.7241 [95% CI, 0.5583-0.8899]). The median number of transfusion units in the control group was 3.0 (adjusted median difference: 3.0 [95% CI, 2.0-4.0]; p-value <0.0001).

PD results were also supportive about the positive impact of pegcetacoplan on relevant clinical parameters.

## *3.3. Uncertainties and limitations about favourable effects*

The main uncertainties regarding pegcetacoplan efficacy results were related to the study design (i.e., the absence of an active comparator and review of data in this open-label context) and the representativeness of the subject population in regard with the claimed indication. The absence of an active comparator was not optimal in terms of efficacy and safety since subjects from the target population have access to C5 inhibition therapy as current SoC.

In addition, the open-label design and the post hoc changes in the SAP further limit the reliability of the conclusions raised on the efficacy of pegcetacoplan. Indeed, the study was unblinded, and it cannot be excluded that changes in study methodology and interpretation were data-driven. This was adequately reflected in the PI, based on the hierarchy of secondary endpoints implemented in the first active version of the protocol.

## *3.4. Unfavourable effects*

The summary of safety profile of pegcetacoplan is updated with the data from completed study APL2-308 in complement inhibitor naïve patients, ongoing LTE study APL2-307 and ongoing paediatric study APL2-PNH-209.

Most common TEAEs in study APL2-308 expressed by the exposure-adjusted rates were: hypokalaemia (21%), pain in extremity (21%), arthralgia (17.5%), dizziness (17.5%), pyrexia (14%), and headache (14%).

In study APL2-308, six subjects in pegcetacoplan experienced SAE (with multiple events recorded). The exposure-adjusted rate of SAEs per 100 subject-years was 21.0 in the pegcetacoplan group.

Injection site reactions (ISRs), infections, haemolytic disorders, thrombosis, hypersensitivity were outlined as adverse events of special interest, which is in accordance to in the initial application identified AESIs. In Study APL2-308, 16 subjects (34.8%) had an injection site reaction. Few subjects (3; 6.5%) required concomitant medication for symptom management. Similar frequencies of ISRs were observed in study APL2-302.

In the overall pegcetacoplan group, 11 subjects (23.9%) had infections. All infection TEAEs except one were mild or moderate in severity (refer to the information on the event of death). There was no pattern observed in types of infections.

There were three moderate to severe events of haemolytic disorders in pegcetacoplan group observed, that led to the increase of dose. No TEAEs of thrombosis were reported during Study APL2-308.

In the overall pegcetacoplan group, 12 subjects (26.1%) had events in the SMQ of hypersensitivity, with most common events in SMQ being erythema (6.5%), rash (4.3%), rash maculo-papular (4.3%).

In addition the 6 TEAEs reported under the OC 'Infections and Infestations' were mild to moderate and resolved without any change in pegcetacoplan dose.

## *3.5. Uncertainties and limitations about unfavourable effects*

The main uncertainties and limitations about unfavourable effects are related to sample size, treatment duration in the SoC group and extrapolation of the safety results presented considering the claimed indication.

True integration of the pivotal trials safety data (APL2-302 and APL2-308) was not possible, because of differences in study design and duration of treatment between the two studies, which is in accordance with the ICH M4E (R2) guidance.

Indeed, the safety database is consisted of 46 subjects who received at least one dose of pegcetacoplan, 11 of them initially allocated to the SoC. On average, subjects who switched to pegcetacoplan received SoC for 55.7 days compared to a mean exposure of 180.1 days for subjects of the experimental arm.

PASS studies using registry data for pegcetacoplan and the ongoing study APL2-307 will provide more data regarding the occurrence of serious infections, the outcomes on pregnancy and the long term safety data.

## *3.6. Effects Table*

**Table 57: Effects Table for Aspaveli in adult patients with PNH who have haemolytic anaemia**

| Effect | Short description | Unit | Treatment N=35 | Control N=18 | Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Hb stabilization | Avoidance of a ≥1 g/dL Hb decrease at W26 | Number of subjects, n (%) | 20 (85.7 %) | 0 (0%) | 95%CI: 0.5720-0.8902<br>p-value <0.0001 | |
| LDH concentration | Change in LDH concentration from baseline to W36 | LS mean change ± SE | -1870 ± 100.971 | -400.09 ± 312.988 | 95%CI: -2113 to -827.32<br>p-value <0.0001 | |
| Hb response | ≥1 g/dL increase in Hb from baseline to W26 | Number of subjects, n (%) | 25 (71.4%) | 1 (5.6%) | 95%CI: 0.3390-0.7431<br>p-value<0.0001 | CSR, RCP |
| Change in ARC | Change in ARC from baseline to W26 | LS mean change ± SD | -123.26 ± 9.164 | -19.44 ± 25.209 | 95%CI: -158.90, -48.74<br>p-value <0.0002 | |
| Change in Hb level | Change in Hb level | LS mean change ± SE | 2.94 ± 0.393 | 0.27 ± 0.75 | 95%CI: 0.99-4.35<br>p-value < 0.0019 | |
| Transfusion need | Proportion of subjects who received transfusion or had decrease of Hb >2 g/dL from baseline to W26 | Number of subjects, n (%) | 4 (11.4%) | 18 (100%) | 95%CI: -0.9041, -0.5969<br>p-value <0.0001 | |
| Transfusion avoidance | Proportion of subjects who do not require a transfusion during the RCP | Number of subjects, n (%) | 32 (91.4%) | 1 (5.6%) | 95%CI: 0.5583, 0.8899<br>p-value <0.0001 | |
| Median number of transfusion | | Number | 3.0 | 0.0 | 95%CI: 2.0-4.0<br>p-value <0.0001 | |
| **Effect** | | **Unit** | **Treatment N=46** | **Control N=18** | **Strength of evidence** | **References** |
| **Unfavourable Effects** | | | | | | |
| 'General disorders and administration site conditions' TEAEs | | Number of subjects, n (%) | 19 (41.3%) | 1 (5.6%) | | |
| 'Metabolism and nutrition disorders' TEAEs | | Number of subjects, n (%) | 11 (23.9%) | 3 (16.7%) | | |
| | | | | | | |
| 'Musculoskeletal and connective tissue disorders' TEAEs | | Number of subjects, n (%) | 10 (21.7%) | 1 (5.6%) | | |
| 'Skin and subcutaneous tissue disorders' TEAEs | | Number of subjects, n (%) | 10 (21.7%) | 0 (0%) | | |
| 'Gastrointestinal disorders' TEAEs | | Number of subjects, n (%) | 7 (15.2%) | 2 (11.1%) | | |
| 'Infections and Infestations' TEAEs | | Number of subjects, n | 8 (17.4%) | 13 (27.8%) | | |

| Effect | Short description | Unit | Treatment N=35 | Control N=18 | Strength of evidence | References |
|---|---|---|---|---|---|---|
| | | (%) | | | | |
| 'Nervous system disorders' TEAEs | | Number of subjects, n (%) | 8 (17.4%) | 0 (0%) | | |
| 'Respiratory, thoracic and mediastinal disorders' TEAEs | | Number of subjects, n (%) | 6 (13.0%) | 3 (16.7%) | | |
| 'Blood and lymphatic disorders' TEAEs | | 3 (16.7%) | 5 (10.9%) | 3 (16.7%) | | |

Abbreviations: ARC=absolute reticulocyte count, CI: confident internal, CSR=clinical study report, Hb=Haemoglobin, LDH=lactate dehydrogenase, RCP=randomized controlled period, TEAE = Treatment-emergent adverse events

Notes: TEAEs are presented as SOC rather than preferred terms (PTs) to emphasize on the differences between groups in this small size study.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The most important efficacy effects associated with pegcetacoplan administration were

- the improvements in Hb stabilization and response which demonstrated the superiority of pegcetacoplan treatment over SoC in stabilizing Hb concentration over 26 weeks.
- The change in LDH concentrations demonstrated the superiority of pegcetacoplan over SoC in controlling IVH.
- the significant reduction of transfusion requirements in the treatment group.

It is also noted that plasma concentrations of pegcetacoplan in PNH patients not treated by C5 inhibitors (either naïve or having stopped C5 inhibitor therapy) can be considered both effective for improving Hb and control of LDH levels. PD results were also supportive about the positive impact of pegcetacoplan on relevant clinical parameters.

Altogether, these data point to a significant improvement of haemolysis management and haematopoiesis status associated with pegcetacoplan treatment, versus supportive care. Additional exploratory results were presented supporting this and the beneficial impact of pegcetacoplan on fatigue and overall QoL.

Considering the SoC only consisted of supportive treatments and that the open-label design could have impacted the review of data, the extrapolation of these results in the target population in which complement inhibitors is the actual SoC was questioned during the assessment. Indeed, the studied population adequately reflected the complement inhibitor-naïve PNH population but the chosen comparator was suboptimal to the EU standards. Extrapolation of the data from non-EU to EU target population is considered acceptable.

Study APL2-308 safety database is limited in terms of size and duration. Comparison with the safety data from study APL2-302 with patients that were treated with C5 inhibitor and known safety profile of pegcetacoplan is done. Overall, in both pivotal studies (APL2-302 and APL2-308) most pegcetacoplan treated participants experienced at least one TEAE, AEs were relatively comparable in two pivotal studies, and the most of AESIs were broadly comparable between pivotal studies. No new safety signals arose and pegcetacoplan safety profile remains manageable.

### 3.7.2. Balance of benefits and risks

The already established safety of pegcetacoplan as in the context of the same underlying disease in complement inhibitor naïve and experienced patients is reassuring, along with justifications provided regarding the extrapolation from the non-EU to the EU target population. The benefit/risk balance is therefore considered positive in the claimed indication.

### 3.7.3. Additional considerations on the benefit-risk balance

None.

## *3.8. Conclusions*

The overall B/R of Aspaveli in the indication as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia is considered positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include treatment of adult patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) not previously treated with a complement inhibitor for ASPAVELI, based on final results from study APL2-308. This is a Phase III, randomized, open-label, comparator-controlled study that enrolled adult patients with PNH who had not been treated with a complement inhibitor. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics Annex II and Package Leaflet and to the Risk Management Plan (RMP).

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.