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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Aspaveli (pegcetacoplan)
Treatment of paroxysmal nocturnal haemoglobinuria
EU/3/17/1873

Sponsor: Swedish Orphan Biovitrum AB (publ)

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain
Other name(s)	-
International Non-Proprietary Name	Pegcetacoplan
Tradename	Aspaveli
Orphan condition	Treatment of paroxysmal nocturnal haemoglobinuria
Sponsor's details:	Swedish Orphan Biovitrum AB (publ) 112 76 Stockholm Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	Best Regulatory Consulting Ltd
COMP opinion	11 April 2017
EC decision	22 May 2017
EC registration number	EU/3/17/1873
Post-designation procedural history	
Transfer of sponsorship	Transfer from Best Regulatory Consulting Ltd to Apellis Ireland Limited – EC decision of 17 April 2019 2nd Transfer from Apellis Ireland Limited to Swedish Orphan Biovitrum AB (publ) – EC decision of 4 June 2021
COMP opinion on review of orphan designation at the time of marketing authorisation	5 November 2021
Type II variation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Selma Arapovic Dzakula
Applicant	Swedish Orphan Biovitrum AB (publ)
Application submission	4 April 2023
Procedure start	22 April 2023
Procedure number	EMA/H/C/005553/II/0011
Invented name	Aspaveli

Proposed therapeutic indication	Aspaveli is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Aspaveli
CHMP opinion	25 January 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Karri Penttila
Sponsor's report submission	25 May 2023
COMP discussion and adoption of list of questions	16-18 January 2024
Oral explanation	14 February 2024
COMP opinion	15 February 2024
Appeal to the COMP opinion procedural history	
COMP rapporteur	Elisabeth Johanne Rook / Joao Rocha
Appeal submission	28 March 2024
Appeal oral explanation	17 April 2024
COMP final opinion	18 April 2024

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2017 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain was considered justified based on preliminary clinical data showing improvement of parameters of haemolysis;
- the condition is life-threatening and chronically debilitating due to the complications of chronic haemolysis, such as abdominal pain, infection, cytopenia, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in different organs. Vascular complications in the central nervous system are the most common cause of death;
- the condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that the proposed product improved haemoglobin levels in patients in whom haemolysis was not controlled by the currently authorized treatment for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain as an orphan medicinal product for the orphan indication: treatment of paroxysmal nocturnal haemoglobinuria".

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2021 was based on the following grounds:

"The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of paroxysmal nocturnal haemoglobinuria (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 0.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the complications of chronic haemolysis, such as abdominal pain, cytopenias, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in various organs. Vascular complications in the central nervous system are the most common cause of death;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Aspaveli may be of potential significant benefit to those affected by the orphan condition still holds. Aspaveli demonstrated statistically significant and clinically meaningful increase in haemoglobin levels and reduced the need for transfusions as compared to the currently authorised products.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Aspaveli (pegcetacoplan), poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain, pegcetacoplan for treatment of paroxysmal nocturnal haemoglobinuria (EU/3/17/1873) is not removed from the Community Register of Orphan Medicinal Products".

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare haematological disorder. It is a clonal haematopoietic stem cell (HSC) disease that presents with haemolytic anaemia, thrombosis and smooth muscle dystonias, as well as bone marrow failure in some cases.

Patients with PNH have clonal blood cells with defective surface expression of various GPI-anchored proteins. GPI is synthesized in the endoplasmic reticulum from phosphatidylinositol through sequential additions of monosaccharide molecules and other components via 11 reaction steps. Nascent GPI-anchored proteins undergo several remodelling reactions in the endoplasmic reticulum and the Golgi apparatus during transport to the cell surface. At the cell surface, the GPI-anchored proteins are primarily localized to microdomains that are rich in glycosphingolipids and cholesterol, termed lipid rafts. In PNH-affected cells, the first step in GPI biosynthesis is defective; as a result, PNH cells have defective surface expression of various GPI-anchored proteins. (Hill et al, Nat Rev Dis Primers. 2017 May 18;3:17028. doi: 10.1038/nrdp.2017.28.)

PNH cells carry a loss-of-function mutation in PIGA. PNH-linked PIGA mutations are somatic mutations, as patients with PNH can harbour blood cells with normal levels of GPI-anchored proteins. PIGA is located on Xp22.2. The X chromosome localization explains why one somatic PIGA mutation can be sufficient to cause GPI deficiency in most patients with PNH, as only one allele is functional in both men and women. The main consequences of clonal expansion of PIGA-mutant HSCs are intravascular haemolysis and thrombosis; bone marrow failure can develop independently and extravascular haemolysis only manifests under eculizumab therapy. Anaemia in PNH is often multifactorial and can result from a combination of haemolysis and bone marrow failure. Abdominal pain, back pain, oesophageal spasm, dysphagia (difficulty swallowing) and erectile dysfunction are common

manifestations associated with haemolytic PNH and are often a direct consequence of intravascular haemolysis and the release of free haemoglobin. Disabling fatigue is a common feature of PNH and can be disproportionate to the degree of anaemia. Fatigue is often most intense during a haemolytic attack but is usually present at all times. Episodes of jaundice and haemoglobinuria are reported by almost 50% of patients. Patients with PNH have an increased risk of chronic kidney disease as a result of long-term intravascular haemolysis. Renal tubular damage can occur from microvascular thrombosis, accumulation of iron deposits or both. Mild-to-moderate pulmonary hypertension has also been reported, but the association between chronic kidney disease and clinically significant pulmonary hypertension is still controversial.

The COMP continues to consider PNH an orphan condition.

The approved extension of therapeutic indication *"ASPAVELI is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia"* falls within the scope of the designated orphan condition "treatment of paroxysmal nocturnal haemoglobinuria".

Intention to diagnose, prevent or treat

The medical plausibility has yet to be confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The condition continues to be chronically debilitating and is associated with higher mortality in patients who do not respond to C5-inhibitor treatment.

Thrombosis is the most common cause of mortality in PNH (accounting for almost 50% of deaths before complement inhibition therapy was introduced). Anaemia in PNH is often multifactorial and can result from a combination of haemolysis and bone marrow failure. Disabling fatigue is a common feature of PNH and can be disproportionate to the degree of anaemia. It is associated with smooth muscle dystonia. Abdominal pain, back pain, oesophageal spasm, dysphagia (difficulty swallowing) and erectile dysfunction are common manifestations associated with haemolytic PNH and are often a direct consequence of intravascular haemolysis and the release of free haemoglobin. Fatigue is often most intense during a haemolytic attack but is always usually present. Episodes of jaundice and haemoglobinuria are reported by almost 50% of patients.

Number of people affected or at risk

The sponsor has identified two European reports published since the sponsor's initial Maintenance designation in December 2020, illustrating the prevalence of PNH in the general population. The two studies used different methods for the identification of cases as well as different definitions of PNH. The Danish study by Hansen et al. (2020) was based on data from the Danish National Patient Register during the period 1977-2016. This register was linked with information regarding death, migration, and demographics from the Danish civil registration system. In this way all diagnoses of PNH in Denmark from hospitalization since 1977 and from outpatient contacts since 1994 were included. All citizens of Denmark constitute the denominator of this nationwide study. In this study, the reported prevalence proportion of PNH in Denmark in 2015 was 0.104/10,000 persons.

The UK study by Richards et al. (2021) was based on data from the Haematological Malignancy Research Network (HMRN) including patients referred for screening with a wide range of clinical indications including PNH. The source population within the HMRN constitutes 3.8 million people.

Prevalence estimates concerned patients with detectable PNH clones in the peripheral blood. This estimate was 0.381/10,000 persons. These two European studies provide up to date evidence that PNH is a very rare condition in the EU. The fairly large difference in estimates from these two studies can be explained largely by differences in definitions of PNH and methods of data ascertainment. The recently published US study (Jalbert et al. 2019) was based on US claims data and is regarding the prevalence of PNH consistent with the European studies with an estimate close to that from the Danish study (0.13/10,000 person).

Table 1. Studies included with PNH prevalence estimates

Reference/Data Source	PNH assessment	Reported Prevalence
Europe		
Hansen et al. 2020 (Denmark)	Hospitalized/outpatient PNH patients, Danish National Patient Register 1977-2016. Source population of approx. 5.5 million	0.104/10,000 (estimate in 2015)
Richards et al. 2021 (HMRN UK)	Patients with detectable PNH clones in the peripheral blood. Source population of 3.8 million. 2004-2018.	0.381/10,000 (overall estimate for the period)
US		
Jalbert et al. 2019	Patients with at least one PNH diagnosis among persons continually enrolled in the Truven US MarketScan Commercial/	

In conclusion, evidence of the prevalence of PNH in the EU are very limited. However, using a conservative approach with a very wide definition of PNH, the prevalence is estimated to be around 0.4/10,000 persons.

During the initial maintenance review of the orphan designation at the time of Aspaveli (EMA/OD/0000051430), the COMP agreed to a prevalence of 0.4/10.000 persons, and since new publications do not contradict that figure it can be retained.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Currently the two products authorised for this condition are Soliris (eculizumab) and Ultomiris (ravulizumab) which are C5 inhibitors. The only curative treatment for PNH is hematopoietic stem cell transplantation (HSCT) using allogeneic donors.

The approved indications of eculizumab and ravulizumab, as reflected in the respective summaries of product characteristics, are as follows:

"Soliris is indicated in adults and children for the treatment of: Paroxysmal nocturnal haemoglobinuria (PNH). Evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (see section 5.1)";

and

"Ultomiris is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):

- in patients with haemolysis with clinical symptom(s) indicative of high disease activity.

- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months (see section 5.1)".

"Aspaveli is already 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 new indication as agreed by the CHMP is: ***ASPAVELI is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.***

Aspaveli is intended for PNH patients with haemolytic anaemia; and Soliris and Ultomiris are intended for PNH patients with haemolysis and clinical symptoms indicative of high disease activity. The COMP considered there is complete overlap with the indications for Soliris and Ultomiris.

This was based on the observation that "high disease activity" as defined for Soliris and Ultomiris is associated with elevated LDH (≥1.5 × the upper limit of normal (ULN)) and haemolytic anaemia. In the case of PNH haemolytic anaemia, it has been observed that an intense haemolysis should be present, but should not be the only criteria, as this might well be rather benign. Therefore, and in line with the evidence available, additional considerations like the presence of relevant symptomatology (e.g. anaemia, dyspnoea, fatigue, abdominal pain, etc) and/ or thrombotic complications should be required to qualify the haemolytic anaemia.

The target population of Aspaveli covers patients with haemolytic anaemia which is captured in its entirety in the indications of Soliris and Ultomiris, therefore both are considered satisfactory methods of treatment for the target patient population of this extension of indication.

Significant benefit

The sponsor has proposed that pegcetacoplan (Aspaveli) offers a clinically relevant advantage to Soliris and Ultomiris. They have provided arguments for the second-line as well as the first-line setting, however, as this extension of indication is for an extension to the first-line setting, only that data will be assessed.

APL2-308 (PRINCE) was a randomized, multicenter, open-label, controlled study with the objective to evaluate the efficacy and safety of pegcetacoplan compared with that of the SoC (standard of care - excluding complement inhibitors) in subjects with PNH not previously treated with a C5 inhibitor.

The study consisted of a screening period of up to 4 weeks, followed by a randomized controlled period (RCP) of 26 weeks. A total of 53 patients with PNH who met all of the inclusion criteria and none of the exclusion criteria were randomized (2:1 ratio) to receive either pegcetacoplan or to remain on their current SoC (excluding complement inhibitors) from Visit 2 (Day 1) to Visit 15 (Week 26).The standard of care group involved 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. Neither eculizumab (Soliris) nor ravulizumab

(Ultomiris) was used in this group. Although the study locations excluded sites in the EU and 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.

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%).

Primary efficacy endpoints:

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

Secondary efficacy endpoints:

- Hb response (yes/no) in the absence of transfusions (Hb response is defined as ≥1 g/dL increase in Hb from baseline at Week 26);
- change from baseline to Week 26 in absolute reticulocyte count (ARC) ;
- change from baseline through Week 26 in Hb concentration ;
- proportion of subjects who received transfusion or had decrease of Hb > 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. Note that the initial definition of transfusion avoidance was modified to be consistent with the definition used in the other Phase 3 PNH study;
- number of packed red blood cells (PRBC) units transfused from baseline to Week 26;
- change from baseline to Week 26 in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue Scale score;
- normalization of Hb concentrations (≥1xLLN) from Baseline to Week 26 in the absence of transfusions (yes/no);
- normalization of LDH concentrations (≤1 × the ULN) from Week 4 through Week 26 in the absence of transfusions (yes/no);
- change from baseline to Week 26 in European Organisation for Research and Treatment of Cancer 30-item QLQ C30 scores.

The results from the primary efficacy endpoints showed the following:

- The proportion of subjects with Hb stabilization (defined as avoidance of a ≥1 g/dL Hb decrease at Week 26) was 85.7% in the pegcetacoplan group.
- The adjusted difference between pegcetacoplan and SoC was with a p-value of<0.0001, demonstrating the superiority of pegcetacoplan treatment over SoC in stabilizing Hb concentration over 26 weeks.

The results from the secondary endpoints showed the following:

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.

For the purpose of establishing a significant benefit it would have been preferential if the control arm would have contained either eculizumab or ravulizimab. Eculizumab has been available and used extensively in Europe as first line therapy as a standard of care.

To date there are no head-to-head studies of pegcetacoplan vs either eculizumab or ravulizumab in the complement inhibitor naïve patients. To assess the relative effectiveness of pegcetacoplan versus C5 complement inhibitors, this sponsor has submitted a matched adjusted indirect comparison (MAIC)

based on a publication by Wong et al 2023 *Comparative Effectiveness of Pegcetacoplan Versus Ravulizumab and Eculizumab in Complement Inhibitor-Naıve Patients with Paroxysmal Nocturnal Hemoglobinuria: A Matching-Adjusted Indirect Comparison.* This publication discussed a comparison in treatment outcomes in complement inhibitor-naive patients with PNH, using individual patient data (IPD) from the pegcetacoplan arm of study APL2-308 (PRINCE) and aggregate data from the ravulizumab and eculizumab arms of study ALXN1210-PNH-301.

It was noted that both studies are randomised, with 53 (APL2-308, IPD data) and 246 (ALXN1210-PNH-301, aggregate data) patients, so the IPD part is quite small. The approach is an unanchored MAIC due to lack of a common control arm.

The patients included in the MAIC:

- ≥ 18 years old;
- naïve to complement inhibitor treatment;
- documented meningococcal vaccinations absolute neutrophil count >500/mm3 at the screening visit;
- adequate platelet count at the screening visit (>50,000/mm3 in the APL2-308 study and >30,000/mm3 in the ALXN1210-PNH-301 study);
- no previous history of bone marrow transplantation.

The PRINCE study excluded patients who had received treatment with any complement inhibitor within 3 months prior to screening, whereas the ALXN1210-PNH-301 study excluded patients with any current or previous exposure to complement inhibitor.

Endpoints were similarly defined in the APL2-308 (PRINCE) and ALXN1210-PNH-301 studies and are shown in Table 2.

Table 2. Comparison of endpoint definitions

Endpoint	APL2-308 (PRINCE) definition	ALXN1210-PNH-301 definition
Change in LDH level	Change in LDH levels from baseline to Week 26	Change in LDH levels from baseline to Week 26 (Day 183)

Endpoint	APL2-308 (PRINCE) definition	ALXN1210-PNH-301 definition
LDH normalization	LDH normalization at Week 26 in the absence of transfusions	Hemolysis as measured by LDH normalization from Days 29 through 183
Time to first LDH normalization	Time to first occurrence of LDH normalization	Time to first occurrence of LDH normalization
Hemoglobin stabilization	Avoidance of a ≥ 2 g/dl decrease in hemoglobin level in the absence of transfusion	Avoidance of a ≥ 2 g/dl decrease in hemoglobin level in the absence of transfusion
Transfusion avoidance	Proportion of patients with transfusion avoidance through Week 26 Study guidelines: transfusions will be administered if hemoglobin is < 7 g/dl without symptoms, or ≥ 7 to< 9 g/dl with symptoms	Proportion of participants who remained transfusion free and did not require a transfusion per protocol-specified guidelines through Week 26 (Day 183) Study guidelines: hemoglobin value ≤ 9 g/dl with signs or symptoms of sufficient severity to warrant a transfusion, or a hemoglobin value ≤ 7 g/dl regardless of presence of clinical signs/symptoms
Transfusion requirements	Total number of units of PRBC transfused from Week 4 to Week 26	Total number of units of PRBC transfused from baseline to Week 26 (Day 183)
Breakthrough hemolysis	≥1 New or worsening sign or symptom of intravascular hemolysis (fatigue; hemoglobinuria; abdominal pain; dyspnea; anemia [hemoglobin<10 g/dl], or MAVEs including thrombosis, dysphagia, or erectile dysfunction) in the presence of LDH ≥ 2 x ULN after prior reduction to < 1.5 x ULN with treatment to Week 26	≥1 New or worsening sign or symptom of intravascular hemolysis (fatigue; hemoglobinuria; abdominal pain; dyspnea; anemia [hemoglobin<10 g/dl]; or MAVEs including thrombosis, dysphagia, or erectile dysfunction) in the presence of LDH ≥ 2 x ULN after prior reduction to < 1.5 x ULN with treatment
MAVEs	Proportion of patients experiencing MAVEs (including thrombosis) to Week 26	Proportion of patients experiencing MAVEs (including thrombosis)
FACIT-Fatigue	Week 26 change from baseline in FACIT-Fatigue score	Week 26 (Day 183) change from baseline in FACIT-Fatigue score
General health status (EORTC QLQC30)	Week 26 change from baseline in general health status EORTC QLQ-C30 score	Week 26 (Day 183) change from baseline in general health status EORTC QLQ-C30 score

Statistical Analysis

To estimate the likelihood of enrolment in the ALXN1210-PNH-301 study versus in the APL2-308 study, a propensity score model based on logistic regression was used to assign weights to each patient in the APL2-308 IPD. Matching was performed such that the weighted means and proportions of baseline characteristics in the PRINCE study IPD matched those of the ALXN1210-PNH-301 study aggregate data. The weight applied to each patient in the APL2-308 IPD was equal to the inverse odds of their enrolment in the ALXN1210-PNH-301 study versus in the APL2-308 study. Separate sets of weights were generated to compare pegcetacoplan to ravulizumab and pegcetacoplan to eculizumab.

Model adequacy was assessed by considering effective sample size (ESS) and through visual inspection of histograms of patient weights. Adequate models were required to have an ESS of at least 50% of the initial APL2-308 study population. Because of sample size limitations, it was not possible to adjust for all effect modifiers. Patients from the APL2-308 study were weighted on Asian race, age at first infusion, female sex, and baseline EORTC general health score.

Before matching, the Wald test with 95% confidence interval (CI) was used to compare categorical and continuous variables (i.e., chi-squared and z tests, respectively). After matching, outcomes were compared between balanced treatment groups using statistical tests that incorporated weights generated during matching. The weighted Wald test with 95% CI was used for comparisons of categorical and continuous variables (i.e., weighted chi-squared and z tests, respectively).

A bias factor analysis was conducted to quantify the extent of residual bias from unmeasured confounders, which provided a set of adjusted results of the unanchored MAIC. A set of potential confounders that were binary baseline variables (e.g., age ≥ 65 years, overweight/obese, history of aplastic anaemia) was selected, and a bias factor was calculated for each. Unanchored indirect comparisons were separately adjusted for each bias factor by subtracting the factor from the effect estimate and 95% CI.

Of the 35 patients from the pegcetacoplan arm of the APL2-308 (PRINCE) study, 34 were included in the analysis, whereas one patient was excluded because of a lack of LDH and haemoglobin data after baseline. After weights were applied to match baseline characteristics of these patients to those of patients in the ravulizumab and eculizumab arms of the ALXN1210-PNH-301 study, the effective sample sizes of the pegcetacoplan arm were 24 and 22, matched to 125 patients from the ravulizumab arm and 121 from the eculizumab arm, respectively.

Before weighting, there were significant differences between the pegcetacoplan and ravulizumab arms in the following baseline characteristics: White race, American Indian or Alaska Native race, mean LDH level, and EORTC QLQ-C30 general health score. Except for the EORTC QLQ-C30 general health score, these characteristics also differed between the pegcetacoplan and eculizumab arms at baseline (Table 3).

After separately weighting the pegcetacoplan arm (on Asian race, age at first infusion, female sex, and EORTC QLQ-C30 general health score) to match the ravulizumab and eculizumab arms, there was a larger proportion of patients who were American Indian or Alaska Native in the pegcetacoplan arm than in the ravulizumab (30.4% vs. 0.8%, $p = 0.0026$) or eculizumab (36.7% vs. 0.8%, $p = 0.0008$) arms. Mean baseline LDH level was also higher in patients who received pegcetacoplan compared with ravulizumab (2,220.27 U/l vs. 1,633.50 U/l, $p = 0.0004$) or eculizumab (2,291.04 U/l vs. 1,578.30 U/l, $p<0.0001$). No other baseline characteristics differed significantly between patients treated with pegcetacoplan versus with ravulizumab or eculizumab after weighting (Table 4).

Table 3. Baseline demographic and clinical characteristics (before weighting)

Characteristic	APL2-308 PRINCE	ALXN1210-PNH-301		P value[a]	
	Pegcetacoplan N= 34 [A]	Ravulizumab N= 125 [B]	Eculizumab N= 121 [C]	[A] vs [B]	[A] vs. [C]
Sex, n (%)					
Male	19 (55.9)	65 (52.0)	69 (57.0)	0.8350	1
Female	15 (44.1)	60 (48.0)	52 (43.0)	0.8350	1
Age at first infusion of study drug, mean ± SD, years	42.7 ± 12.5	44.8 ± 15.2	46.2 ± 16.2	0.4166	0.1833
Race, n (%)					
Asian	23 (67.6)	72 (57.6)	57 (47.1)	0.3887	0.0544
White	0 (0.0)	43 (34.4)	51 (42.1)	<0.0001*	<0.0001*
Black or African American	2 (5.9)	2 (1.6)	4 (3.1)	0.2006	0.613
American Indian or Alaska Native	8 (23.5)	1 (0.8)	1 (0.8)	<0.0001*	<0.0001*
Other[b]	1 (2.9)	4 (3.2)	4 (3.3)	1	1
Not reported/unknown	0 (0.0)	3 (2.4)	4 (3.3)	1	0.5767
Weight, mean ± SD, kg	65.3 ± 13.4	68.2 ± 15.6	69.2 ± 14.9	0.2731	0.1393
Height, mean ± SD, cm	164.6 ± 7.7	166.3 ± 9.0	166.2 ± 10.7	0.2717	0.3291
Time from PNH diagnosis to consent, mean ± SD/median (range), years[c]	5.8 ± 5.96	3.8 (0, 41)	3.9 (0, 34)	–	–
No PRBC unit transfusions received within 1 year before study entry, n (%)	5 (14.7)	23 (18.4)	21 (17.4)	0.8045	0.9111
LDH, mean ± SD, U/l[d]	2092.4 ± 902.3	1633.5 ± 778.8	1578.3 ± 16.2	0.0069*	0.0009*
Hemoglobin, mean ± SD, g/dl[e]	9.6 ± 1.4	9.4 ± NR	9.60 ± NR	0.3909	1
General health status EORTC QLQ-C30 score at baseline	64.5 ± 18.8	56.1 ± 20.3	57.5 ± 20.3	0.0241*	0.0614
Physical functioning EORTC QLQ-C30 score at baseline	81.6 ± 14.6	76.6 ± 17.1	76.4 ± 17.6	0.0903	0.0819
Fatigue symptoms EORTC QLQ-C30 score at baseline	36.3 ± 20.0	39.3 ± 22.7	37.3 ± 23.4	0.4473	0.7992

EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; *LDH* lactate dehy- drogenase; *NR* not reported; *PNH* paroxysmal nocturnal hemoglobinuria; *PRBC* packed red blood cell; *SD* standard deviation
*Significant *p* values
a *p* values for continuous and categorical variables were calculated with the Wald test (i.e., *z* and chi-squared tests, respectively)
b Subjects in the ALXN1210-PNH-301 study who identified as being multiple races were included in this category
c The ALXN1210-PNH-301 study reported range and the PRINCE study reported SD; the *p* value was not calculated because the measures of variability did not match
d Normal range, 120–246 U/l
e Normal range, 12.3–15.3 g/dl for women and 14.0–17.5 g/dl for men. The *p* value was not calculated because SDs were not reported in the ALXN1210-PNH-301 study.

Table 4. Baseline demographic and clinical characteristics (after weighting)[a]

	PRINCE Study		ALXN1210-PNH-301 study		P value [d,e]	
	Pegcetacoplan [b]	Pegcetacoplan [c]	Ravulizumab	Eculizumab		
Analysis sample, *n*	34	34	125	121		
Effective sample size, *n*	24	22	–	–		
Characteristic	[A]	[A']	[B]	[C]	[A] vs. [B]	[A'] vs[C]
Sex, %						
Male	52.0	57.0	52.0	57.0	0.8350	1
Female	48.0	43.0	48.0	43.0	~	~
Age at first infusion of study drug, mean ± SD, years	44.8 ± 13.4	46.2 ± 13.6	44.8 ± 15.2	46.2 ± 16.2	~	~
Race, %						
Asian	57.6	47.1	57.6	47.1	~	~
White	0.0	0.0	34.4	42.1	–	–
Black or African American	7.6	10.7	1.6	3.1	0.3057	0.3398
American Indian or Alaska Native	30.4	36.7	0.8	0.8	0.0026*	0.0008*
Other[f]	4.4	5.4	3.2	3.3	0.7995	0.7039
Not reported/unknown	0.0	0.0	2.4	3.3	–	–
Weight, mean ± SD, kg	66.8 ± 14.3	66.9 ± 14.5	68.2 ± 15.6	69.2 ±14.9	0.6304	0.414
Height, mean ± SD, cm	165.0 ± 6.8	165.5 ± 6.6	166.3 ± 9.0	166.2 ±10.7	0.3618	0.6483
Time from PNH diagnosis to consent, mean ± SD/median (range), years[g]	6.6 ± 5.95	6.2 ± 5.8	3.8 (0, 41)	3.9 (0, 34)	–	–
No packed PRBC unit transfusions received within 1 year before study entry, %	13.8	12.1	18.4	17.4	0.5692	0.4553
LDH, mean ± SD, U/l[h]	2220.3 ± 883.7	2291.04 ± 967.38	1633.5 ± 778.8	1578.3 ± 16.2	0.0004*	<0.0001*
Hemoglobin, mean ± SD, g/dlI	9.7 ± 1.4	9.6 ± 1.4	9.4 ± NR	9.6 ± NR	0.2674	0.9598
General health status EORTC QLQ-C30 score at baseline	56.1 ± 18.0	57.5 ± 18.2	56.1 ± 20.3	57.5 ± 20.3	~	~
Physical functioning EORTC QLQ-C30 score at baseline	80.0 ± 14.7	80.6 ± 15.0	76.6 ± 17.1	76.4 ± 17.6	0.2438	0.1694
Fatigue symptoms EORTC QLQ-C30 score at baseline	42.1 ± 20.6	42.4 ± 21.7	39.3 ± 22.7	37.3 ± 23.4	0.4953	0.2351

Questionnaire; LDH lactate dehydrogenase; NR not reported; PNH paroxysmal nocturnal hemoglobinuria; PRBC packed red blood cell; SD standard deviation
*Significant p values
a The following baseline characteristics were used for weighting: Asian race, age at first infusion, female sex, and baseline EORTC QLQ-C30 general health score
b Weighted for comparison with the ravulizumab cohort

c Weighted for comparison with the eculizumab cohort
d p values for continuous and categorical variables were calculated with the Wald test (i.e., z and chi-squared tests, respectively). The p value was not calculated for variables used for matching; ' ~ ' is shown in these cases
e p values could not be calculated for categorical variables with 0.0% of patients matched; ' ~ ' is shown in these cases
f Subjects in the ALXN1210-PNH-301 study who identified as being multiple races are included in this category
g The ALXN1210-PNH-301 study reported range and the PRINCE study reported SD; the p value was not calculated because the measures of variability did not match
H Normal range, 120–246 U/l
I Normal range, 12.3–15.3 g/dl for women and 14.0–17.5 g/dl for men. The p value was not calculated because SDs were not reported in the ALXN1210-PNH-301 study.

Clinical and Hematologic Endpoints

After weighting, treatment with pegcetacoplan was associated with statistically significant improvements in most clinical and hematologic endpoints compared with ravulizumab or eculizumab treatment, see Figures 1, 2, 3, 4 (Figures 6, 7, 8, 9 from sponsor's report).

Figure 6 Unanchored comparisons between pegcetacoplan and ravulizumab – LDH endpoints. The following baseline characteristics were used for weighting: Asian race, age at first infusion, female sex, and baseline EORTC general health score. *Significant *p* values

Figure 1.

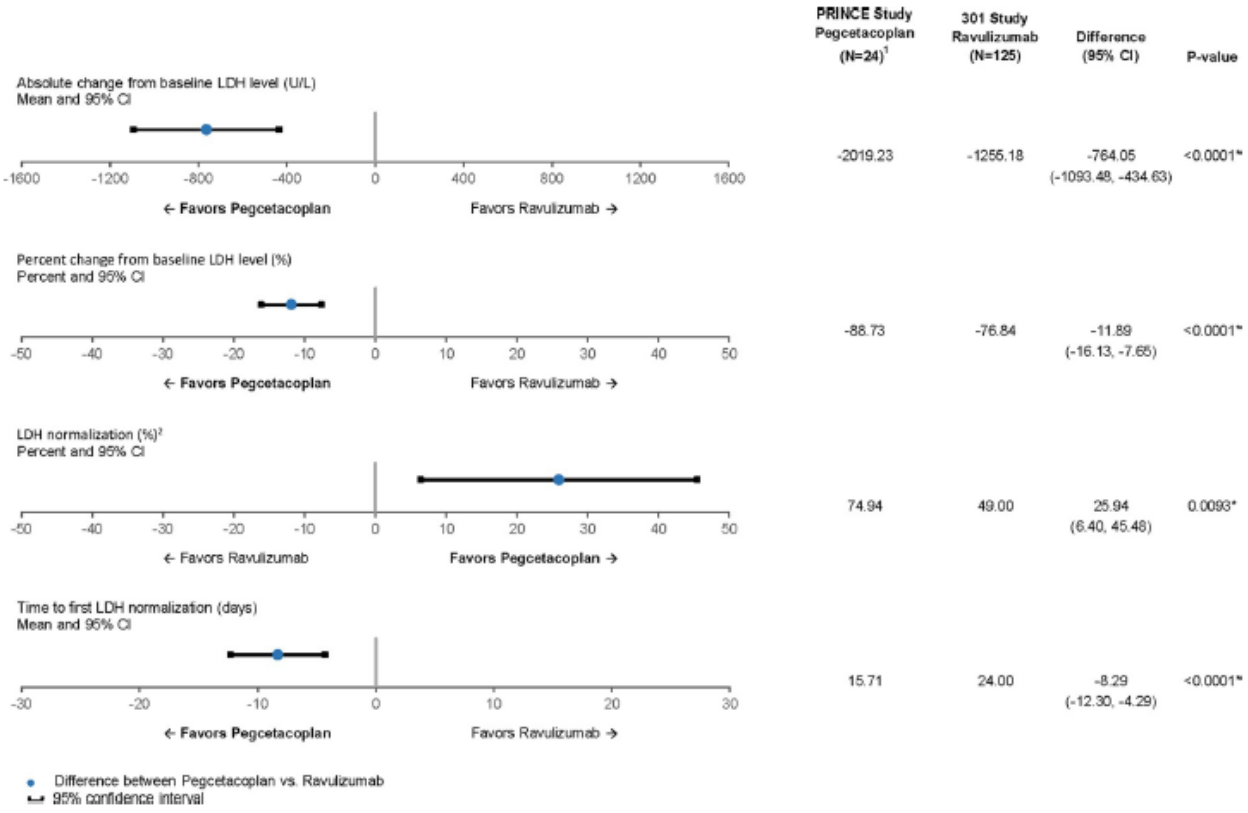


Figure 2.

Figure 7 Unanchored comparisons between pegcetacoplan and eculizumab – LDH endpoints. The following baseline characteristics were used for weighting: Asian race, age at first infusion, female sex, and baseline EORTC general health score. **Significant p values*

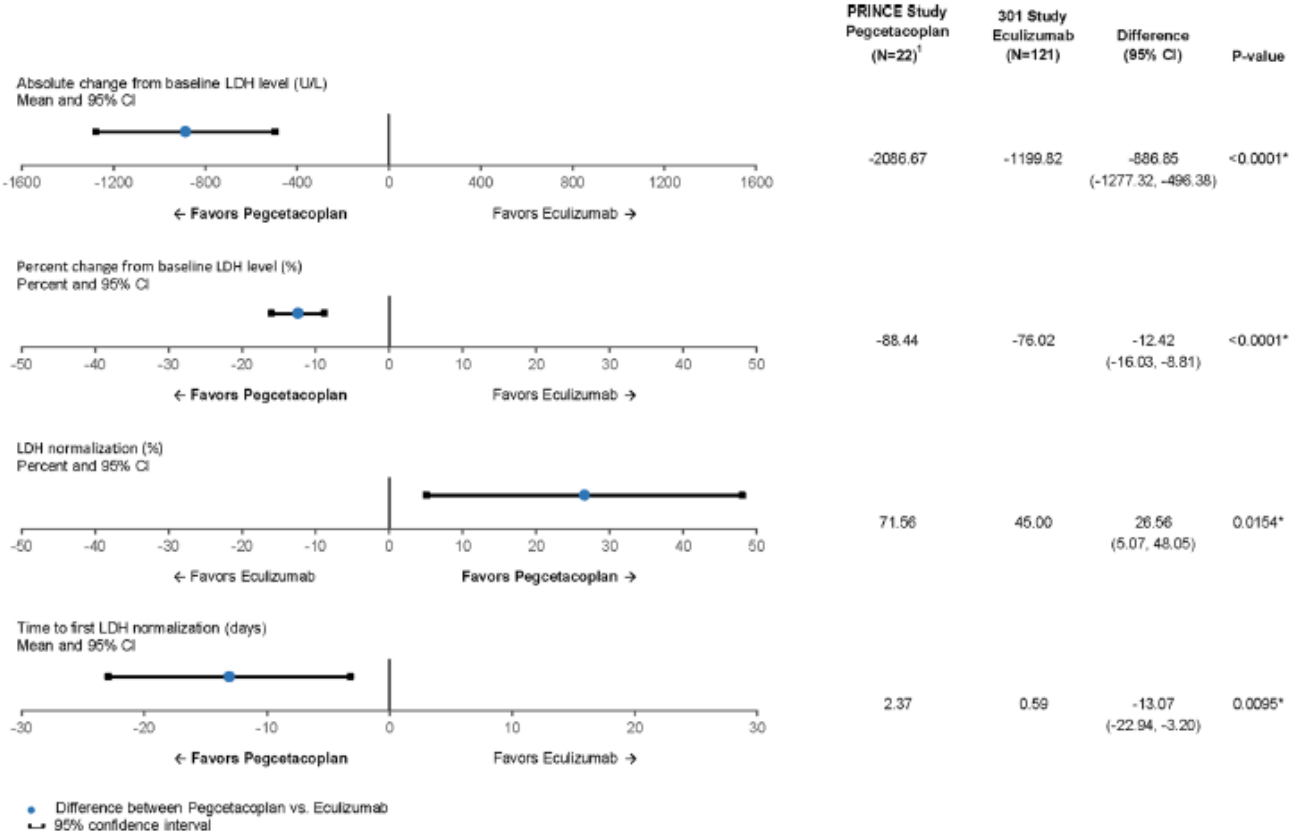


Figure 3.

Figure 8 Unanchored comparisons between pegcetacoplan and ravulizumab – hematologic endpoints. 1. The following baseline characteristics were used for weighting: Asian race, age at first infusion, female sex, and baseline EORTC general health score. 2. Change in hemoglobin level in the ALXN1210-PNH-301 study was estimated from values for percent hemoglobin stabilization and mean hemoglobin levels reported by Lee et al 2019 and Schrezenmeier et al. 2021. *Significant p values

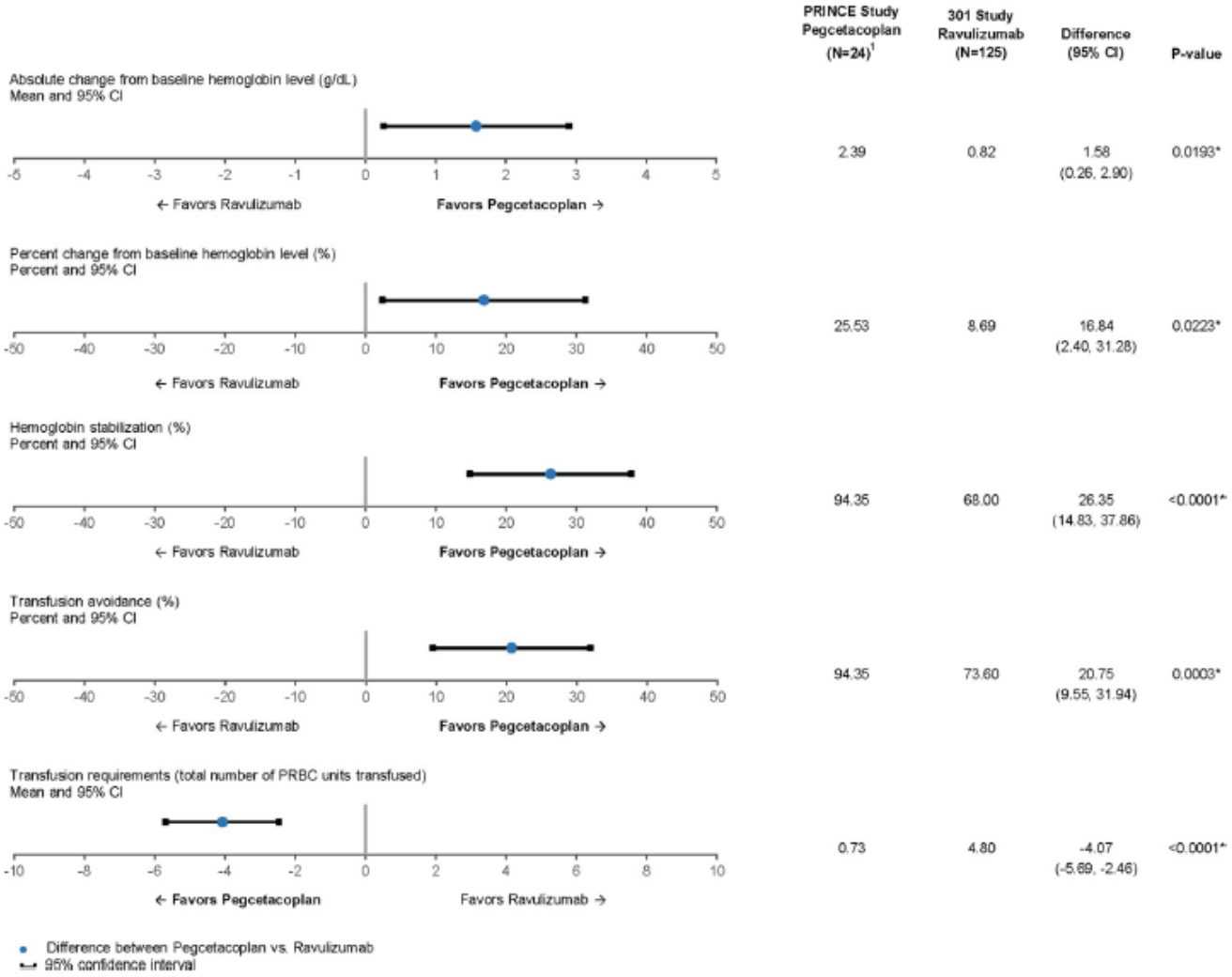
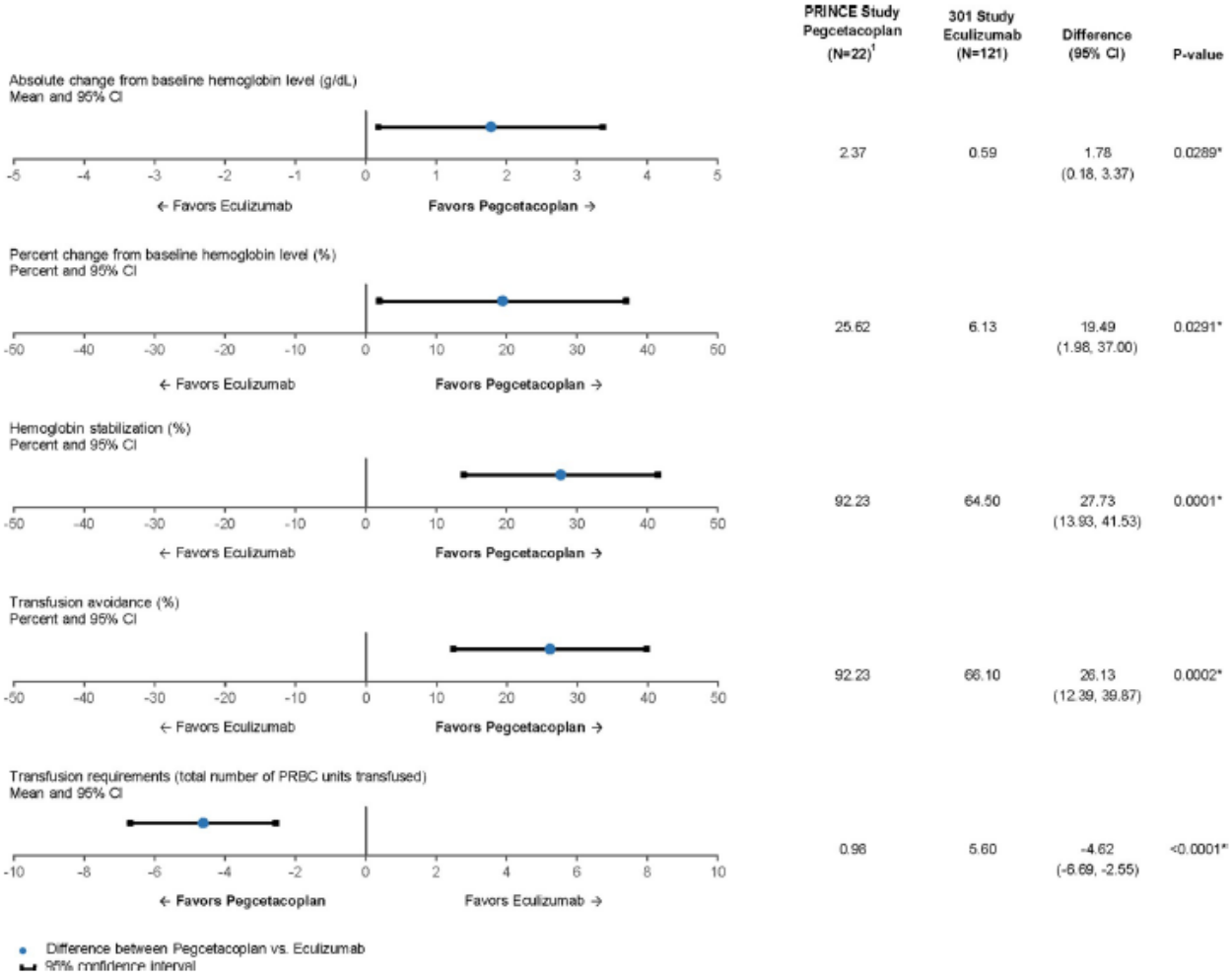


Figure 4.

Figure 9 Unanchored comparisons between pegcetacoplan and eculizumab – hematologic endpoints. 1. The following baseline characteristics were used for weighting: Asian race, age at first infusion, female sex, and baseline EORTC general health score. 2. Change in hemoglobin in the ALXN1210-PNH-301 study was estimated from values for percent hemoglobin stabilization and mean hemoglobin levels reported by Lee et al 2019 and Schrezenmeier et al. 2021. **Significant p values*



The sponsor highlighted the following limitations to the MAIC: The interpretation of this study's results is subject to limitations. MAICs only account for cross-trial differences that are observable in the data (Signorovitch et al 2012). The comparator trial was selected with the aim of minimizing cross-trial differences in design and conduct, but there were still differences between the two studies that could not be adjusted for by statistical analyses (e.g., route of administration and treatment administration schedule).

Because of differences across studies, not all potential effect modifiers could be used as weighting variables. As an unanchored MAIC, it was assumed that absolute treatment effects were constant at any given level of effect modifiers and prognostic variables, which were themselves accounted for. Like all MAICs, the validity of this study relied on the implicit assumption of the internal validity of the studies being compared (i.e., the APL2-308 [PRINCE] and ALXN1210-PNH-301 studies).

Lastly, the IPD of the APL2-308 (PRINCE) study were weighted to match the aggregate data of the ALXN1210-PNH-301 study for the purpose of comparison; therefore, the results may not be fully generalizable to other PNH patient populations.

The Committee concurred with the sponsor's conclusion regarding the lack of alignment in the baseline characteristics regarding race and LDH which differ across studies. It was concluded that the matching had only a limited impact on the results, as an ESS reduction was seen. It was also noted that patients from the APL2-308 study were weighted on Asian race, age at first infusion, female sex, and baseline EORTC general health score. The description of the analysis was considered to be high-level; details were omitted.

It appears that the two studies are better aligned in terms of the endpoint definitions, however, some variables are not well balanced between treatment arms and the matching seemed not to have worked well for all variables. The Committee noted that there was no description of the underlying methods that were used for the analysis, no discussion on the validity of the analysis, no sensitivity analysis, nothing on the weighting, ESS and intermediate steps that are part of a MAIC analysis, as well as what were the assumptions and whether they were met. These key elements and data are important for establishing significant benefit and have not been clearly presented in the submission.

The COMP considered that the sponsor should further elaborate on the MAIC between study APL2-308 (PRINCE) (Wong et al, 2023) and aggregate data from the ravulizumab and eculizumab arms of study ALXN1210-PNH-301 as well as present any additional data which could support significant benefit in first line treatment.

4. COMP list of issues

Significant Benefit

The COMP noted that the PRINCE study (APL2-308) which was submitted as supporting data did not include patients on C5 complement inhibitors in the standard of care comparator arm. In order to overcome this limitation a MAIC has been submitted for the first line treatment. This MAIC compared APL2-308 (PRINCE Study) to the ALXN1210-PNH-301 in an unanchored way due to the lack of a common comparator arm and involved data in complement inhibitor-naïve patients with paroxysmal nocturnal haemoglobinuria.

The COMP considered that more details regarding the methodology and analysis (e.g., a description of the methods that were used for the analysis; what are the underlying assumptions and were the assumptions met?; what is the impact of baseline differences between the trials?; a discussion on the validity of the analysis; were sensitivity analysis carried out and do they confirm the results?; elaboration on the weighting, ESS and intermediate steps that are part of a MAIC analysis) should be provided for the proposed conclusion of significantly better outcomes to be understood.

The sponsor is invited to further elaborate how this MAIC, and any additional data could support the basis of a clinically relevant advantage to C5 inhibitors (eculizumab and ravulizumab) which would support the basis of significant benefit.

Comments on sponsor's response to the COMP list of issues

The sponsor provided a written response which is summarised below.

The sponsor stated that a systematic literature review was performed to identify the most suitable comparator trial for APL2-308. Two individuals independently screened 895 studies and extracted data from publications and concluded that ALXN1210-PNH-301 met eligibility criteria.

Independent patient data (IPD) from APL2-308 were weighted using a form of propensity scores generated by method of moments to match aggregate data from ALXN1210-PNH-301. After applying weights to IPD, two unanchored comparisons were performed:

1) pegcetacoplan vs ravulizumab,
2) pegcetacoplan vs eculizumab.

The effective sample size (ESS) was calculated as the squared sum of individual weights divided by the sum of squared weights. Weighting adjusted the population of the IPD so that it was more similar to that of the aggregate data. The sponsor noted that although there is no established definitive threshold for a minimum ESS, general scientific practice suggests > 50%- 75%. A review of MAICs in technology appraisals submitted to UK National Institute for Health and Care Excellence (NICE) reported a median reduction in ESS from the original sample size of 74.2%. They also note that in another MAIC study, ESS of ≥50% of the original sample was specified (Bhak RH, et al. Curr Med Res Opin. 2021;37(11):1913-23). The original sample size for the pegcetacoplan cohort was 34, and ESS after weighting was 24 (vs ravulizumab) and 22 (vs eculizumab) (i.e., ESS of 71% and 65% of the original sample size, respectively). The sponsor also highlighted that adding more weighting variables would have further reduced ESS, resulting in a small number of patients in the IPD influencing the results and leading to loss of precision in the effect estimates.

Confounding bias was minimised by:

- Ensuring alignment between compared trials based on study design and inclusion/exclusion criteria.
- Weighting IPD from APL2-308 on aggregate baseline patient characteristics from ALXN1210-PNH-301.

Observable differences between trials were adjusted for to the extent possible on balance of precision. They indicated that residual confounding from observable covariates was possible due to skewness in distribution and different covariate forms. The sponsor claims that it was not possible to account for unobserved difference and that a bias factor analysis was performed to estimate the effects of unmeasured confounders (i.e., variables relevant to patient outcomes not reported in the aggregate data but available in IPD).

Additionally, a new meta-analysis of the combined MAICs was submitted. Meta-analysis combining results of two separate MAICs (pegcetacoplan vs ravulizumab and pegcetacoplan vs eculizumab) was performed to generate a single treatment effect estimate for each endpoint of interest.

- I^2 statistic was used to quantify the magnitude of heterogeneity.
- Because heterogeneity was considered low ($I_2 \approx 0\%$), a fixed-effect model was used to weight each set of comparisons based on the inverse of the variance of each effect estimate.

The MAIC study results showed that patients receiving pegcetacoplan have:

- Significant reduction in LDH levels from baseline: −815.11 U/l, p<0.0001 compared with the aggregate data for ravulizumab and eculizumab.
- Significantly higher proportion achieved LDH normalization: 26.24%, p=0.0003 compared with the aggregate data for ravulizumab and eculizumab.
- Significantly greater increase in haemoglobin levels from baseline: 1.66 g/dl, p=0.0014 compared with the aggregate data for ravulizumab and eculizumab.

- Significantly higher proportion achieved haemoglobin stabilization: 27.01%, p<0.0001 compared with aggregate data for ravulizumab and eculizumab.
- Significantly higher proportion to avoid transfusions: 23.33%, p<0.0001 compared with aggregate data for ravulizumab and eculizumab.

Results of the meta-analysis were consistent with those of the published MAIC (Wong et al. 2023)

Clinical improvements in clinically relevant endpoints were significantly greater with pegcetacoplan than with C5 inhibitors (ravulizumab and eculizumab) in complement inhibitor-naïve patients with PNH:

- Greater absolute and percent reductions in LDH levels from baseline.
- Larger proportion of patients with LDH normalisation.
- Greater absolute and percent increases in haemoglobin levels from baseline.
- Larger proportion of patients with haemoglobin stabilisation.
- Larger proportion of patients avoiding transfusion.

The COMP assessed the above-provided response of the sponsor.

During the oral explanation the COMP noted that the key assumption of no unmeasured confounding between the two trials APL2-308 and ALXN1210-PNH-301 could only be partly met in this MAIC analysis. While the sponsor tried to align the trials on eligibility criteria and weighted on measured baseline factors, it was observed that there could still be residual differences on difficult-to-measure variables like disease severity, genetics, adherence levels etc. that could act as confounders.

Sensitivity analyses were conducted, estimating the potential magnitude and direction of bias from residual confounding. These, however, could not definitively account for unmeasured factors leading to some untestable uncertainty that remains around fully meeting the no unmeasured confounding assumption. Furthermore, the effective sample size (ESS) drops far below 75% (approx. 40%) if all relevant and known prognostic factors/confounders are accounted for which means that there still could be substantial differences between the trial populations.

It was also observed that despite weighing on measured baseline factors, there may be residual systematic differences between the APL2-308 and ALXN1210-PNH-301 trial populations that impact relative efficacy estimates. Sensitivity analyses gauge potential magnitude of bias but cannot account for unmeasured confounding between trials. There was therefore the possibility of residual bias from population differences that could affect relative treatment effect estimates, a limitation of the MAIC methodology. Additional real-world comparative evidence could have helped confirm the findings.

The APL2-308 trial included only 18 patients in the standard of care (SoC) arm compared to 34 patients receiving pegcetacoplan in the ALXN1210-PNH-301 trial. This small sample size reduces reliability of the results from the standard of care arm as a comparator as well as from the pegcetacoplan arm. With so few patients, outcomes could have been disproportionately influenced by outliers. Any imbalances in patient related factors between arms could also occur more likely due to chance with smaller samples, even after statistical adjustment techniques. The committee noted that the ESS becomes quite small once all known covariables are accounted for. This means that the trial populations are not consistent/overlapping, leading to additional uncertainty as the ESS gets significantly smaller. The insufficient amount of data hindered the ability to explore the heterogeneity of treatment effects across subgroups within the SoC arm. Larger real-world datasets could have helped contextualise findings.

While the MAIC compared endpoints like LDH, hemoglobin and transfusion outcomes, some committee members considered that while the increase in haemoglobin could be clinically relevant, there are still doubts about the validity of this observation due to the above-discussed limitations.

Without prejudice to the above, and for completeness, it bears highlighting that additional real-world patient-reported outcome data on symptom burden, disability, work/social life impact, treatment adherence challenges, healthcare utilization etc. could have helped confirm if the efficacy differences found translated into meaningful benefits for patients' daily wellbeing. (Shammo J et al, Journal of Blood Medicine 2022:13 425–437)

The COMP concluded that the responses to the question raised regarding the unanchored MAIC could not adequately address their concerns regarding the clinically relevant advantage and thus significant benefit could not be established. The Committee therefore could not recommend maintaining the orphan designation.

5. COMP negative opinion adopted on 15 February 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of paroxysmal nocturnal haemoglobinuria (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the complications of chronic haemolysis, such as abdominal pain, cytopenia, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in various organs. Vascular complications in the central nervous system are the most common cause of death;
- the sponsor's claim that Aspaveli is of significant benefit to those affected by the orphan condition was not established. Significant benefit over Soliris and Ultomiris was claimed on the grounds of a clinically relevant advantage;
- the sponsor provided unanchored matched adjusted indirect comparison of Aspaveli versus Soliris and Ultomiris. A significant difference in efficacy could not be established due to methodological uncertainties related to (i) the small sample size which was further reduced in the MAIC effective sample size, and (ii) the assumptions underlying the unanchored adjusted comparison. Due to these methodological issues, the results presented were inconclusive in establishing a clinically relevant effect regarding the magnitude of the effect on key variables such as haemoglobin and Lactate dehydrogenase which are associated with outcome measures which are specific to the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are not satisfied.

The Committee for Orphan Medicinal Products has recommended that Aspaveli, Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain, pegcetacoplan for treatment of paroxysmal nocturnal haemoglobinuria (EU/3/17/1873) is removed from the Community Register of Orphan Medicinal Products.

6. Appeal to the negative opinion adopted on 15 February 2024

Grounds for appeal

The sponsor presented detailed grounds for appeal (EMA/OD/0000172113) on 28 March 2024.

Please refer to the sponsor's appeal documents in the case *Input from Industry* folder.

The detailed grounds for appeal were further addressed by the sponsor at an oral explanation before the COMP on 17 April 2024.

Comments on the grounds of appeal

In the grounds for appeal the sponsor presents further information to support the significant benefit of pegcetacoplan vs ravulizumab and vs eculizumab based a claim for a clinically relevant advantage due to improved efficacy in the broad PNH indication, now also comprising the first-line treatment setting in C5-inhibitor naïve patients.

In brief, in the grounds for appeal, the sponsor presented further justification for the original unanchored MAIC as method for indirect comparison (despite uncomplete matching for LDH, race, and the small sample size) and discusses the clinical relevance of these MAIC results. The sponsor also explained why no alternative and more robust method Network meta-analysis (NMA) was conducted. In addition, the sponsor presented a new MAIC analysis and a simulated treatment comparison (STC), which included baseline LDH as a matching variable. Further supportive data are presented to demonstrate the expected benefit of pegcetacoplan over C5 inhibitors eculizumab and ravulizumab which include data from real-world studies in patients who switched from a C5 inhibitor to pegcetacoplan, and side-by-side comparisons of the main efficacy outcomes from the two phase III RCTs in the first- and second-line treatment settings.

The sponsor also offers mechanistic arguments on benefits of pegcetacoplan which are equally applicable in the broad PNH population (first-/second-line): While C5-inbibitors are mechanistically associated with excessive complement-3 opsonization of red blood cells, which could lead to EVH (extra-vascular haemolysis), this is prevented with the use of Aspaveli because of the higher upstream blockade of the complement system.

The sponsor did not number the grounds for appeal, but for ease of interpretation, the main arguments are grouped into 6 different grounds.

Ground #1 Justification for the original MAIC as method for indirect comparison

The MAIC was conducted using data for pegcetacoplan from the PRINCE study and for eculizumab and ravulizumab from the "ALXN1210-PNH-301" study. These studies had comparable inclusion criteria. As regards the matching of relevant baseline characteristics, statistically significant differences remained for American Indian or Alaska Native race, White patients and baseline LDH levels. It was not possible to minimise these imbalances by weighting as this would have caused a too significant drop in the effective sample size (ESS). However, according to the sponsor these parameters were not expected to have a clinically relevant impact on the MAIC analysis.

The COMP agreed with the sponsor that according to the literature an imbalance in race as such may not have had a large impact on the MAIC outcomes as race in itself is not reported to be a relevant prognostic factor in this disease. While regional differences may still exist, these are rather due to different eligibility to the disease-modifying complement inhibitors (not authorised or reimbursed).

Nevertheless, < 1% of the Japanese patients are reported to have an intrinsic resistance due to impaired binding of ecu/ravulizumab, due to the R885H C5 gene polymorphism (N Engl J Med. (2014) 370:632–9). But this does not likely impact the action of Aspaveli, or would have a large impact on the MAIC, as it is ultra-rare. During the oral hearing the sponsor confirmed that such polymorphisms were not considered to be a relevant factor in the population of the PRINCE study.

Furthermore, the sponsor argued that the imbalances of LDH levels at baseline among the studies would not likely have a relevant impact on the outcomes of the comparative analyses. All groups in the MAIC analysis had baseline LDH levels that were several times higher than the 1.5 × ULN criterion, consistent with ongoing IVH at baseline (Table 3 above). The sponsor states that at such grossly elevated LDH levels, any numeric differences do not translate into clinical differences in severity. This can be seen by the similarity in baseline haemoglobin levels and transfusion needs in the previous 12 months for all three populations before weighting (Table 3 above), and in the similar baseline haemoglobin, transfusion needs and EORTC QLQ-C30 general health score despite residual imbalances after weighting (Table 4 above). However, the COMP pointed out that LDH is an acknowledged biomarker of ongoing haemolysis, and also associated with the risk of break-through haemorrhages and thrombotic events. The COMP notes the sponsors effort to address this potential issue by conducting an additional MAIC analysis with matching based on LDH levels. See below ground #3 for the outcomes.

The sponsor also explained the reasons for not performing a network meta-analysis (NMA). These mainly included the lack of studies with a comparative control arm as applied in the PRINCE study, and/or significant differences in the study populations regarding inclusion criteria. This included also the Phase 3 trial comparing eculizumab and placebo (TRIUMPH study). Although a NMA is considered more robust from a methodological perspective, the rationale of the sponsor was acknowledged by the COMP.

Ground #2 clinical relevance of the differences in effects among treatments (from the MAIC)

Results from the MAIC suggested that pegcetacoplan was associated with statistically significant improvements in **LDH levels, LDH normalisation, haemoglobin levels, haemoglobin stabilisation and transfusion avoidance** versus ravulizumab and eculizumab in patients with complement-inhibitor naïve PNH. The magnitude of the treatment differences in LDH and haemoglobin were clinically meaningful. The improvement in haemoglobin levels was equivalent to the transfusion of at least one unit of packed red blood cells (PRBCs), and more patients had their LDH normalised, which likely reduced their risk of serious PNH complications. Please refer to above Figures 1, 2, 3, and 4 which show the efficacy outcome of the original MAIC analysis, demonstrating significant improvements in most clinical and haematologic endpoints compared with ravulizumab or eculizumab treatment. The COMP agreed that as such, the magnitude of the effect sizes in increased haemoglobin levels and normalisation of LDH levels are clinically relevant, acknowledging also that anaemia is a key complication of PNH. The relevance of the haematological outcomes is also supported by improvement in QoL and fatigue scores. It is agreed with the sponsor that reduced need for blood transfusions is clinically important, as these are burdensome and potential harmful for patients (e.g. iron accumulation). Uncertainty, however, remains on the true effect size, given the small number of patients available for the MAIC.

Ground #3 New statistical analysis: MAIC matched for LDH at baseline

An additional MAIC analysis was conducted by the sponsor to account for between-trial differences in baseline LDH. According to the sponsor, all the known effect modifiers with clinical relevance were used to balance the populations of patients who received the target treatments. The MAIC which

included baseline LDH as an adjustment variable indicated an effective sample size of 48% to 69% (see Table 5 below), which is less than the original MAIC analyses. The number of adjustment variables was kept to a minimum to preserve sample size as much as possible (see Table 5 below). Compared with the original MAIC, race (Asian) and baseline EORTC were not included as adjustment variables for the clinical haematology outcomes, while race (Asian), age and sex were not included as adjustment variables for patient-reported outcomes. There is no evidence to indicate that race is an effect modifier for patients with PNH, see discussed above.

Table 5. Adjustment of variables and effective sample sizes

		Before weighting, n (%)	After weighting: ESS, n (%)	
Outcomes	**Baseline adjustment variables**	**Pegcetacoplan**	**Pegcetacoplan (vs ravulizumab)**	**Pegcetacoplan (vs eculizumab)**
• Absolute reduction in LDH • LDH normalisation • Absolute haemoglobin change • Transfusion avoidance	Baseline LDH; sex; age	34 (100)	24 (69)	21 (61)
• EORTC QLQ-C30 global health score	Baseline LDH; baseline EORTC	34 (100)	17 (50)	16 (48)

For the MAIC including LDH, the mean of the weights were 0.68–0.80 and the median of the weights were 0.48–0.60.

The results from this analysis (Table 6) were largely consistent with the original MAIC data (see above Figures 1, 2, 3, and 4) for change from baseline in haemoglobin levels, transfusion avoidance and change from baseline in EORTC QLQ-C30 general health score. While the magnitude of treatment difference for change from baseline in LDH levels was lower in this new analysis, the rate of patients achieving LDH normalization was increased with pegcetacoplan as compared to the original MAIC. This might be expected, since the matching was done towards the lower baseline reference level of study "ALXN1210-PNH-301", facilitating the achievement of LDH normalization.

Table 6. Treatment differences for pegcetacoplan versus C5 inhibitors in the MAIC analyses with the inclusion of LDH as a matching variable.

	Treatment difference	
	Pegcetacoplan versus eculizumab	**Pegcetacoplan versus ravulizumab**
CFB in LDH levels, U/L, MD (95% CI)	−134.37 (−193.51, −75.24)	−138.02 (−215.26, −60.77)
Proportion of patients with LDH normalisation, %, RD (95% CI)	43.80 (33.32, 54.28)	39.80 (28.91, 50.69)
CFB in haemoglobin levels, g/dL, MD (95% CI)	1.56 (0.39, 2.73)	1.42 (0.37, 2.47)
Proportion of patients with transfusion avoidance, RD (95% CI)	20.32 (4.56, 36.08)	14.14 (−0.26, 28.54)
CFB in EORTC QLQ-C30 global health score, MD (95% CI)	9.39 (−0.64, 19.41)	10.68 (0.21, 21.15)

Abbreviations: CFB, change from baseline; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LDH, lactate dehydrogenase; MAIC, matched adjusted indirect comparison; MD, mean difference; RD, risk difference

The COMP agreed that the results of these additional analyses which adjusted for baseline variables including LDH level, were broadly consistent with the original MAIC data. However, also for this new MAIC analysis methodological uncertainties remain, mainly owing to the heavy down-weighting of patients (i.e. approx. half of the patients for both ravulizumab and eculizumab are assigned weights below 0.5, while ideally this value should be close to 1) and significant reduction in the ESS, as compared to the original sample size. This may further support the view that the populations in the PRINCE and the ALXN1210-PNH-301 study are difficult to compare.

Ground #4 New statistical analysis: Simulated Treatment Comparison (STC)

In order to further evaluate the relative efficacy of pegcetacoplan versus ravulizumab and eculizumab and address the shortcomings of the MAIC analyses, a simulated treatment comparison (STC) has been conducted. The STC allowed adjustment of multiple baseline characteristics, including LDH.

Table 7. Baseline factors used for adjustment of patient populations in the MAIC and STC.

MAIC	STC
Sex, age, race (Asian) and/or EORTC general health score	Baseline EORTC QLQ-C30 general health score,[a] **Baseline LDH**, sex, age, race (Asian), **baseline haemoglobin, weight, height and/or zero transfusions before enrolment**

[a] Baseline EORTC was not used for adjustment of clinical laboratory parameters (e.g. haemoglobin and LDH) in the STC as EORTC is a patient-reported outcome and should not have direct impact on clinical laboratory values. Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LDH, lactate dehydrogenase; MAIC, matched adjusted indirect comparison; STC, simulated treatment comparison. Bold = additional factors not used in the MAIC

Results of the STC suggested that pegcetacoplan was associated with statistically significant improvements versus eculizumab and ravulizumab which included the following clinically relevant outcomes: an increase in the proportion of patients with LDH normalisation from baseline, an increase in haemoglobin levels from baseline, an increase in proportion of patients with transfusion avoidance from baseline and an increase in EORTC QLQ-C30 general health score from baseline (Table 8).

Table 8. Summary of results for pegcetacoplan versus eculizumab or ravulizumab generated by STC.

	Treatment difference	
	Pegcetacoplan versus eculizumab	**Pegcetacoplan versus ravulizumab**
Proportion of patients with LDH normalisation, %, RD (95% CI)	**47.40 (37.21, 57.59)**	**45.10 (35.37, 54.83)**
CFB in LDH levels, U/L. MD (95% CI)	−159.18 (−200.05, −118.31)	−164.82 (−228.54, −101.10)
Percentage CFB in LDH levels, MD, (95% CI)	−7.58 (−15.32, 0.16)	−7.16 (−15.46, 1.14)
CFB in haemoglobin levels, g/dL, MD (95% CI)	**1.96 (0.99, 2.93)**	**1.76 (0.88, 2.64)**
Percentage CFB in haemoglobin levels, MD (95% CI)	20.39 (9.37, 31.42)	18.75 (8.72, 28.77)
Proportion of patients with transfusion avoidance, %, RD (95% CI)	**28.70 (16.97, 40.43)**	**20.90 (9.78, 32.02)**
CFB in EORTC general health score, MD, (95% CI)	**16.60 (6.31, 26.89)**	**15.10 (5.37, 24.83)**

Abbreviations: CI, confidence interval; CFB, change from baseline; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LDH, lactate dehydrogenase; MD, mean difference; RD, risk difference; STC, simulated treatment comparison.

Results of the STC were generally consistent with those from the MAIC in terms of showing a positive effect on most clinical parameters in favour of pegcetacoplan and in terms of magnitude of effect, except for the probability of LDH normalisation. While the results on this parameter point in the same positive direction for both types of analyses (MAIC and STC), the magnitude of the treatment effects across the methods are substantially different. The STC analysis suggests a much better effect on LDH normalisation for both comparisons (i.e. 47.4% in favour of pegcetacoplan versus eculizumab and 45.1% in favour of pegcetacoplan versus ravulizumab) as the original MAIC analysis (i.e. 26.6% in favour of pegcetacoplan versus eculizumab and 25.9% in favour of pegcetacoplan versus ravulizumab). Whether this is due to the method itself or due to the fact that the STC uses additional baseline factors that were not used in the MAIC analyses was not fully clear to the COMP. Since the STC is a regression-based technique, outcomes are predicted based on the baseline values and since the population in the PRINCE study was more severe than the one from the "ALXN1210-PNH-301" study, the prediction for such patients would assume a better outcome. While the COMP noted that overall the results of the STC analysis were consistent with those from the MAIC in terms of showing a positive effect on most clinical parameters in favour of pegcetacoplan, this additional analysis did not help to decrease the existing methodological uncertainty from the original MAIC analysis. This is because the simulation steps of the STC introduced additional variation associated with even stronger assumptions (including on the correlation and shape of baseline risks and outcome response distributions) than the MAIC analyses.

Ground #5 Clinical data with pegcetacoplan (including real-world evidence and long-term follow-up data)

Two Phase 3 randomized controlled studies (RCTs) have evaluated the efficacy and safety of pegcetacoplan in PNH: in complement inhibitor-naïve patients with PNH (PRINCE study), and in complement inhibitor-experienced patients with PNH (PEGASUS study). These trials showed that pegcetacoplan increased haemoglobin levels (and the rate of haemoglobin stabilisation) compared with

standard of care (SoC) or continued eculizumab treatment (Table 9). In addition, the reduction in LDH levels at follow-up was superior in patients treated with pegcetacoplan versus SoC or eculizumab. Similarly, transfusion avoidance, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score and EORTC QLQ-C30 general health score were all improved with pegcetacoplan compared with SoC or eculizumab. Overall, these crude data are largely consistent with the MAIC and STC results and indicate pegcetacoplan is associated with improvements in clinical and patient-reported outcomes compared with eculizumab or SoC.

Table 9. Summary of clinical and patient-reported outcomes in patients treated with pegcetacoplan from Phase 3 studies.

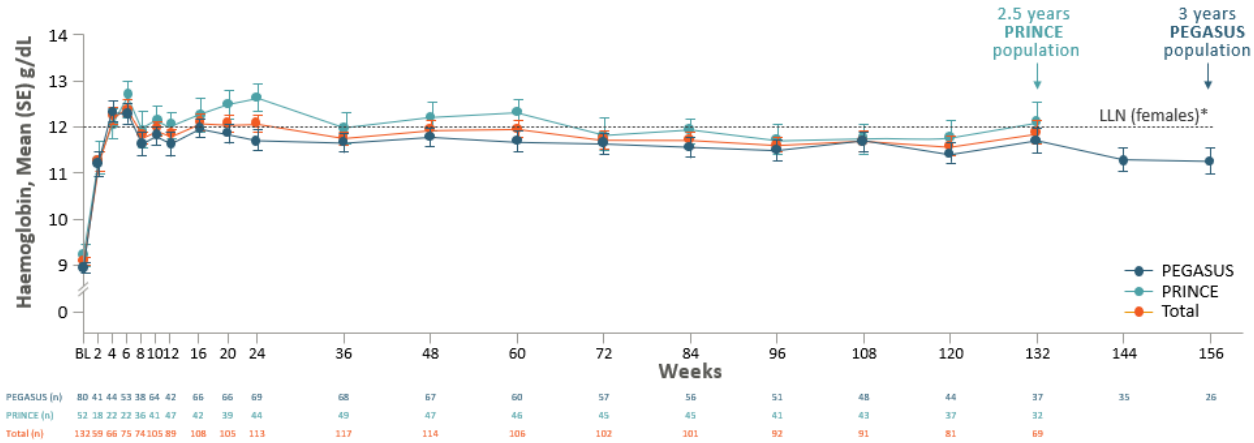
	Complement inhibitor-naïve PNH: PRINCE study (Wong et al., 2023)				**Complement inhibitor-experienced PNH: PEGASUS study (Hillmen et al., 2021)**			
	Baseline		**Week 26**		**Baseline**		**Week 16**	
	PEG (n=35)	SoC[a] (n=18)	PEG (n=35)	SoC[a] (n=18)	PEG (n=41)	ECU (n=39)	PEG (n=37)	ECU (n=38)
Haemoglobin, g/dL (mean)[b]	9.4	8.7	12.8	9.8	8.7	8.7	11.5	8.6
Patients with haemoglobin stabilisation, n (%)	–	–	30 (85.7)	0 (0)	–	–	–	–
LDH, U/L (mean)	2151	1946	205	1535	257.5	308.6	–	–
LDH, U/L CFB, LS mean (SE)	–	–	–1870.5 (101.0)	–400.1 (313.0)	–	–	−15 (42.7)	−10 (71.0)
Patients with LDH normalisation, n (%)[c]	–	–	23 (65.7)	0 (0)	–	–	29 (70.7)	6 (15.4)
Patients with transfusion avoidance, n (%)[d]	–	–	32 (91.4)	1 (5.6)	–	–	35 (85)	6 (15)
FACIT-Fatigue score CFB, LS mean (SE)	–	–	7.8 (1.2)	3.3 (2.1)	–	–	9.2 (1.6)	−2.7 (2.8)
EORTC QLQ-C30 general health score CFB, LS mean (SE)	–	–	18.9 (2.9)	−2.9 (5.7)	–	–	–	–

[a]Control group patients received supportive care (eg, transfusions, corticosteroids, and supplements [iron, folate, and vitamin B12]); [b]Defined as ≥1-g/dL increase from baseline to Week 26; [c]LDH levels ≤ULN (226 U/L) at Week 26; [d]Patients who received a transfusion, escaped from the control group to pegcetacoplan treatment, withdrew from study before Week 26, or were lost to follow-up were categorised as non-responders
Abbreviations: CFB, change from baseline; EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactase dehydrogenase; LS, least squares; PEG, pegcetacoplan; SE, standard error; SoC, standard of care

Importantly, the sponsor also presented long-term follow-up data from their PEGASUS, PRINCE and extension study 307. This data suggests that the positive effects of pegcetacoplan on key clinical and hematologic parameters are maintained (de Castro et al., 2023). As an example, the sponsor presented the long-term data on mean haemoglobin levels which were maintained for up to 3 years (Figure 5).

Indirect comparisons regarding the maintenance of efficacy versus C5-inhibitors are not made, but as discussed in detail under ground #6 below, the effects of C5-inhibitors on anaemia may decline due to development of EVH.

Figure 5. Long term effects of pegcetacoplan on mean haemoglobin levels (up to 3 years)



Results from the two phase 3 RCTs and the MAIC and STC analyses are further supported by two real-world studies in which patients were switched from C5-inhibitors (mainly eculizumab) to pegcetacoplan (Wilson et al., 2024; Fishman et al., 2023). Overall, these data suggest an improvement in clinical (haemoglobin and LDH) and patient-reported outcomes following initiation of pegcetacoplan in routine clinical practice (Table 10).

Table 10. Summary of clinical outcomes, HRQoL and resource utilisation in patients treated with pegcetacoplan from real-world evidence studies.

	Adelphi Real World PNH Disease Specific Programme (Wilson et al., 2024)[a]		OPERA study (Fishman et al., 2023)[b]	
	Baseline	At data collection	Baseline	At last follow-up
	n=61	n=61[c]	n=35	n=35[d]
Haemoglobin, g/dL (mean [SD])	9.0 (1.5)	11.5 (1.6)	8.9 (1.8)	12.3 (1.7)
Patients with LDH ≥1.5 × ULN, %	70.0	42.6	–	–
Patients with physician-perceived moderate or severe fatigue, %	80.4	13.1[e]	–	–
Physician-perceived HRQoL rated very good or excellent, %	42.6	57.4	–	–

[a]Study conducted in France, Italy, Germany, Spain, and the USA; [b]Study conducted in the USA; [c]Patients treated for 1.3 to 14.8 months; [d]Median (IQR) follow-up of 8.0 (5.5) months; [e]Moderate in all cases;
Abbreviations: CI, confidence interval; ER, emergency room; HRQoL, health-related quality of life; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal

In addition, real-world data from a Spanish cohort was presented during the oral hearing. This dataset comprised 6-month efficacy data from 24 PNH patients with unsatisfactory response to C5 inhibitor treatment (at baseline) who were switched to pegcetacoplan (Vallejo C, *et al*. ASH 2023 (abstract 5653), see Table 11. The data showed a substantial increase in haemoglobin levels and improvement in haemolytic parameters (inc. a reduction in LDH and acute haemolytic episodes) as well as a substantial reduction in transfusion needs 6 months after pegcetacoplan treatment has been initiated. It was specifically pointed out that the direct antiglobulin test, indicating extravascular haemolysis (EVH), turned negative in 80% of patients that had a positive test before pegcetacoplan has been initiated, see Table 11. Likewise, (considerable) reductions in median absolute reticulocyte count and total bilirubin levels have been observed in patients treated with pegcetacoplan. This is consistent with

the mechanistic advantage of proximal complement inhibition by pegcetacoplan as compared to terminal complement inhibition by C5 inhibitors, further discussed below. Of note, at the end of the analysis, all 24 patients continued on pegcetacoplan.

Table 11. Real world data with pegcetacoplan from Spanish cohort (second-line setting)

	Pre-PEG	Post-PEG
Hemoglobin (g/dL) [median (range)]	9.1 (5.5-12.1)	12.1 (7.2-14.5)
Absolute reticulocyte count (/mcL) [median (range)]	190,000 (31,000-296,300)	56,000 (4,000-120,000)
Total bilirubin (mg/dL) [median (range)]	1.5 (0.4-6.8)	0.8 (0.2-5.5)
LDH (UI/L) [median (range)]*	316 (124-1,210)	187 (87-856)
LDH / ULN [median (range)]	1.2 (0.5-4.8)	1.0 (0-4)
LDH / ULN > 1.5 (patients)	8 (34.8%)	1 (4.3%)
PRBC transfusion needs (patients)	15 (65.2%)**	4 (17.4%)***/****
Acute hemolytic episodes (patients)	7 (30.4%)**	3 (13%)***
Direct antiglobulin test positivity (patients)	15/22 (68.2%)*****	3/15 (20%)******
PNH clone size (white cells) [median (range)]	98.3% (31-100%)	98.1% (53-100%)

* 6 months before starting PEG. ** 6 months after starting PEG.
*** Three of the four patients have a concomitant disease affecting erythropoiesis: aplastic anemia (1), myelodysplastic syndrome (1), suspected solid neoplasia (1)
**** Not performed in one patient
***** Among patients in which it was positive pre-PEG
Abbreviations: C5i, C5 inhibitor; EVH, extravascular haemolysis; LDH, lactate dehydrogenase; PEG, pegcetacoplan; PNH, paroxysmal nocturnal hemoglobinuria; PRBC, packed red blood cells; QoL, quality of life; ULN, upper limit of normal.

Ground # 6 Pharmacological/biological plausibility

The sponsor further discusses the mechanistic advantages of pegcetacoplan as compared to the C5 inhibitors eculizumab and ravulizumab.

Treatment with C5 inhibitors reduces IVH but can predispose to EVH due to C3 opsonisation (Hill et al., 2017). It has been shown that upon treatment with eculizumab a substantial proportion of red blood cells have bound C3 on their surface (Risitano et al., 2009). Since eculizumab blocks the complement pathway at the level of C5, the earlier steps of the complement cascade, including activation, deposition, and proteolytic cleavage of C3 to C3b, are not affected by eculizumab. Consequently, CD55-deficient PNH red cells become overloaded with C3 fragments and get recognised by complement receptor-bearing macrophages in the spleen and liver. This leads to EVH. In contrast, proximal complement inhibitors like pegcetacoplan, which targets C3, does not induce EVH (Kaudlay et al., 2013). It has been estimated that about 39% of patients treated with eculizumab in the last 6 months still suffering from persistent anaemia (8 to 10 g/dL) and dependent on blood transfusions (Debureaux et al 2021). And 20% of C5 inhibitor-treated patients require transfusions because of EVH (Hill et al., 2017; Risitano et al., 2019).

Pegcetacoplan targets C3, a complement pathway component upstream of C5. Inhibiting proximal complement activity with pegcetacoplan controls C5-mediated intravascular haemolysis as well as C3-mediated extravascular haemolysis. Therefore, it is plausible that the improved clinical outcomes observed in the MAIC, STC, real-world studies and the head-to-head study of pegcetacoplan vs eculizumab in complement 5 inhibitor experienced patients (PEGASUS) are likely related to mechanistic differences between pegcetacoplan and the C5 inhibitors. This mechanistic advantage may be relevant in both first- and second-line treatment in PNH.

Overall COMP conclusion

Although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Aspaveli is of significant benefit to those affected by the orphan condition is established.

Significant benefit over Soliris and Ultomiris was claimed on the grounds of a clinically relevant advantage. In the context of the appeal, the sponsor presented additional data and arguments to the COMP to substantiate the claim of significant benefit of Aspaveli over Soliris and Ultomiris. These include additional analyses of indirect comparisons of efficacy, new data on maintenance of efficacy, and real-world evidence.

Based on the totality of new and previously presented data, the COMP concluded that while uncertainties inherent to the sample size, assumptions and employed methodology of these indirect comparative analyses exist, the overall results on key clinical outcome parameters exhibited the existence of a clinically relevant advantage of Aspaveli over Soliris and Ultomiris. There is a strong biological plausibility. Imbalances of LDH at baseline among studies were not in favour of Aspaveli. A clinically meaningful and stable increase in haemoglobin levels and hence reduced need for transfusions in the first line setting in treatment-naïve patients was shown, as established before in patients with inadequate response to prior Complement 5 inhibitors.

The COMP considered that these data were sufficient to establish a clinically relevant advantage of Aspaveli also in the first-line treatment setting and adopted a final positive opinion.

7. COMP final position on review of criteria for orphan designation adopted on 18 April 2024

Based on the assessment of the detailed grounds for appeal and the argumentations presented by the sponsor during the oral explanation, the COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of paroxysmal nocturnal haemoglobinuria (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the complications of chronic haemolysis, such as fatigue, abdominal pain, cytopenia, and kidney malfunction, and due to occurrence of thrombosis and haemorrhage in various organs. Vascular complications in the central nervous system are the most common cause of death;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Aspaveli is of significant benefit to those affected by the orphan condition is established. Significant benefit over Soliris and Ultomiris was claimed on the grounds of a clinically relevant advantage;
- in the context of the appeal, the sponsor presented additional data and arguments to the COMP to substantiate the claim of significant benefit of Aspaveli over Soliris and Ultomiris. These include additional analyses of indirect comparisons of efficacy, new data on maintenance of efficacy, and real-world evidence. Based on the totality of new and previously presented data, the COMP concluded that while uncertainties inherent to the employed methodology of these indirect comparative analyses exist, the overall results on key clinical outcome parameters exhibited the existence of a clinically relevant advantage of Aspaveli over Soliris and Ultomiris. Specifically, this comprises a clinically meaningful and stable increase in haemoglobin levels and hence reduced need for transfusions in the first line setting in treatment-naïve patients.

The COMP, having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The COMP recommends that Aspaveli, Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-,15,15'-diester with N-acetyl-L-isoleucyl-L-cysteinyl-L-valyl-1-methyl-L-tryptophyl-L-glutaminyl-L-.alpha.-aspartyl-L-tryptophylglycyl-L-alanyl-L-histidyl-L-arginyl-L-cysteinyl-L-threonyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N6-carboxy-L-lysinamide cyclic (2.fwdarw.12)-(disulfide); where two identical synthetic peptide domains are covalently linked at the ends of the polyethylene glycol chain, pegcetacoplan for treatment of paroxysmal nocturnal haemoglobinuria (EU/3/17/1873) is not removed from the Community Register of Orphan Medicinal Products.