13 December 2021
EMADOC-1700519818-744521
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) Stockholm 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
Transfer of sponsorship	Transfer from Apellis Ireland Limited to Swedish Orphan Biovitrum AB (publ)– EC decision of 4 June 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Selma Arapovic Dzakula
Applicant	Swedish Orphan Biovitrum AB (publ)
Application submission	10 September 2020
Procedure start	01 October 2020
Procedure number	EMA/H/C/5553/0000
Invented name	Aspaveli
Proposed therapeutic indication	*Aspaveli is 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* Further information on Aspaveli 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	14 October 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Armando Magrelli
Sponsor's report submission	21 December 2020 from Apellis Ireland Limited before transfer
COMP discussion and adoption of list of questions	7-9 September 2021 and 5-7 October 2021
Oral explanation	N/A
COMP opinion	05 November 2021

2. Grounds for the COMP opinion

Orphan medicinal product designation

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

- 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.

3. Review of criteria for orphan designation at the time of marketing authorisation

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 the

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 designate PNH as an orphan condition.

The approved therapeutic indication "Aspaveli is 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" falls within the scope of the designated orphan condition "Treatment of paroxysmal nocturnal haemoglobinuria"

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by a 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 eculizumab 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 usually present at all times. Episodes of jaundice and haemoglobinuria are reported by almost 50% of patients.

Number of people affected or at risk

The sponsor has provided a prevalence estimate using a very limited number of publications as well as a reference to Orphanet which is not recommended in the current guidance.

Table 1

Reference/Data Source	Reported Prevalence	Extrapolated EU Prevalence per 10,000
Hill et al. 2006	59 people in the UK within a 15-year period	0.15
Schubert et al. 2012	The UK and France the prevalence rate is estimated to be 0.016/10,000	0.016
Griffin et al. 2017	15.9 per million in Europe	0.159
Orphanet 2020	The prevalence is estimated at 1/80,000 in France	0.125

Abbreviations: EU = European Union; PNH = paroxysmal nocturnal haemoglobinuria; UK = United Kingdom.

On the basis of these references the sponsor concluded that the prevalence was between 0.005 and 0.1 per 10,000.

The COMP requested that the sponsor provide a more thorough prevalence calculation. In the revised calculation the sponsor reviewed the literature and reported on two European reports which were published after the Orphan Designation maintenance report was submitted in December 2020. The first; Hansen et al. (2020) was based on data from the Danish National Patient Register during the period 1977-2016. In this study, the reported prevalence proportion of PNH in Denmark in 2015 was 0.104/10,000 persons. The second; a 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. Prevalence estimates concerned patients with detectable PNH clones in the peripheral blood. This publications estimate was 0.381/10,000 persons. These two European studies provide more recent 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 sponsor concluded that by using a conservative approach with a very wide definition of PNH, the prevalence is estimated to be around 0.4/10,000 persons, which the COMP agreed with.

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 eculizumab and ravulizumab which are C5 inhibitors. The only curative treatment for PNH is hematopoietic stem cell transplantation (HSCT) using

allogeneic donors. Recent articles have highlighted some of the challenges faced with the treatment of this condition. Notably the issue of the two different forms of classical and PNH associated with aplastic anaemia have been described (Devalet et al 2015, European Journal of Haematology 95 (190–198). Some of the limitations of the use of eculizumab are discussed in a recent article by Lucio Luzatto in 2016 (F1000Research 2016, 5(F1000 Faculty Rev):209 Last updated: 23 FEB 2016). In this article he presents in diagrammatic form some of the limitations to the use of eculizumab (please see figure 1).

Figure 1.

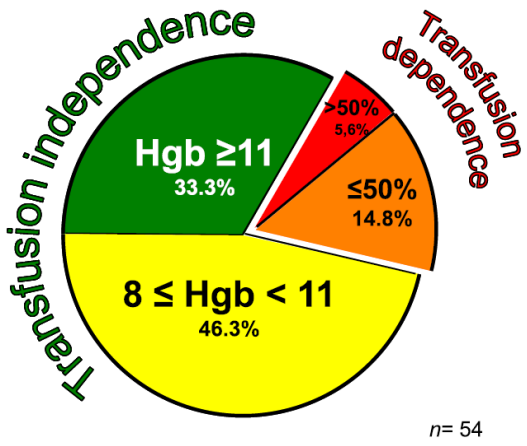


Figure 1. Variable hematological response to eculizumab treatment (modified from 18).

Since the introduction of eculizumab therapy, patients with PNH can live a relatively normal lifespan and patients with haemolytic PNH receiving eculizumab have a more favourable prognosis than patients with a more profound bone marrow failure component, such as aplastic anaemia. The reason for this difference is that eculizumab does not treat the underlying production deficit in the bone marrow. (Hill et al 2017)

For completeness, 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)*".

It bears recalling that the approved indication for Aspaveli is: "*Aspaveli is 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 COMP considered that eculizumab and ravulizumab are satisfactory methods of treatments as the target patient populations of these products (in what concerns paroxysmal nocturnal haemoglobinuria (PNH)) overlap with the target patient population for which Aspaveli is intended. For both C5 inhibitors it is expected that a duration up to 6 months would be needed to achieve a full treatment effect. Aspaveli can be started already after 3 months of treatment, and there is no recommendation to stop treatment with eculizumab or ravulizumab at that time. Therefore, there is a full overlap with the patient population for the approved treatments eculizumab and ravulizumab.

Significant benefit

During the development of pegcetaloplan, Apellis asked a specific question about maintenance of significant benefit in their 2017 protocol assistance procedure (EMEA/H/SA/3633/1/2017/PA/SME/III). COMP provided feedback that the sponsor's preliminary clinical data showed that their product improved haemoglobin levels in patients in whom haemolysis was not controlled by the currently authorised treatment for the condition. The COMP agreed that a positive outcome would support the significant benefit based on a clinically relevant advantage for the patients affected by the condition.

Although C5 inhibition controls intravascular haemolysis (IVH), it does not prevent extravascular haemolysis (EVH) due to C3 fragment deposition on PNH RBCs, but instead increases it, leading to further haemolysis (Risitano et al. 2009; Risitano et al. 2019). The presence of low haemoglobin (Hb) levels, elevated reticulocyte counts, elevated bilirubin levels, continued need for transfusions despite C5 inhibition and relatively well-controlled LDH levels, and persistent patient-reported fatigue are indicators of ongoing disease activity.

There is a significant medical need for an alternative treatment option in patients with PNH which addresses EVH due to C3 fragment deposition on PNH red blood cells (RBCs).

Pegcetacoplan is a complement C3 inhibitor that addresses both the IVH and EVH of PNH by providing upstream inhibition of the complement cascade. Although eculizumab and ravulizumab share a similar mechanism of action, the structure and mechanism of action of pegcetacoplan is different from these 2 therapies. It binds to human C3 and C3b, resulting in proximal inhibition of the complement cascade and control of both IVH and EVH, leading to additional clinical outcomes to currently used C5 inhibitors in patients with PNH.

To support significant benefit the sponsor has provided clinical data from their Phase III study. Study APL2-302 is a Phase 3, prospective, randomised, multicentre, open-label, active comparator-controlled study. The objective of this study was to confirm the treatment efficacy and safety of pegcetacoplan monotherapy for the treatment of PNH in subjects aged ≥18 years who were receiving eculizumab therapy but continued to have Hb levels <10.5 g/dL.

In particular, the comparative efficacy on the anaemia aspect of the condition which is not addressed adequately through the treatment with currently approved C5 inhibitors was presented. The primary endpoint analysis measured change from baseline (CFB) to Week 16 in Hb level. The between treatment group comparison was performed using mixed-model repeated measures (MMRM) analysis. The difference between pegcetacoplan and eculizumab mean Hb CFB to Week 16 was calculated along with its 2-sided 95% CI and associated P value from the MMRM model. Sensitivity and supportive analyses of the primary endpoint were also performed.

For the analyses of key secondary endpoints, non-inferiority was concluded if the appropriate limit of the 95% 2-sided CI indicated that pegcetacoplan was non inferior to eculizumab by the defined noninferiority margin (NIM) for each endpoint. The key secondary endpoints were tested in a hierarchical manner after statistical significance was reached for the primary endpoint.

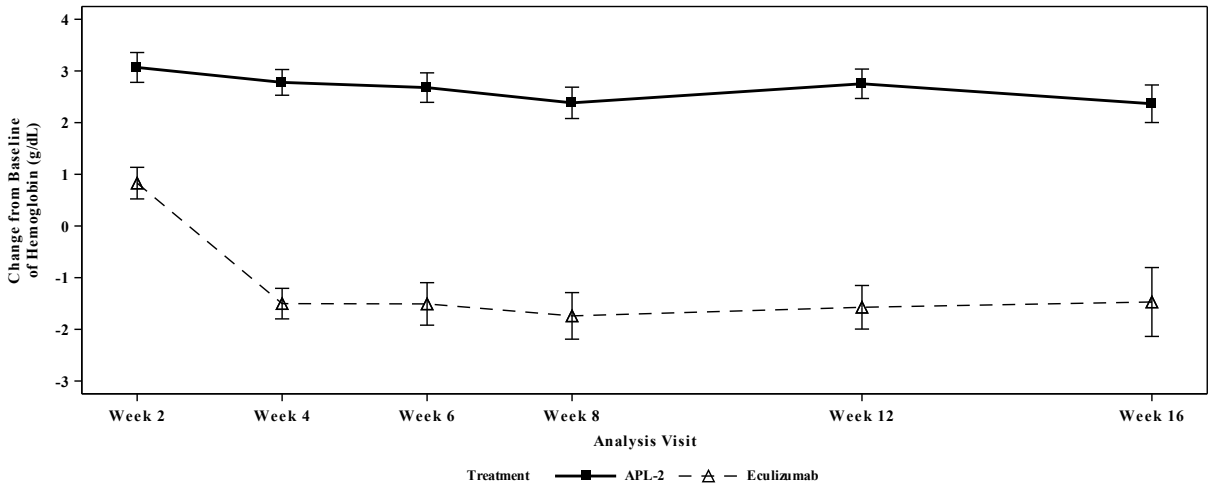
All censoring was due to intercurrent events (ICE). Considerations for ICE were (1) any subject who received a transfusion, discontinued study treatment, or withdrew from the study, and (2) for any subject who received a transfusion or withdrew from the study, all subsequent values were set to missing for the following measurements: Hb value, absolute reticulocyte count (ARC), lactate dehydrogenase (LDH) level, bilirubin level, haptoglobin level, FACIT (Functional Assessment of Chronic Illness Therapy)-Fatigue score, Linear Analog Scale Assessment (LASA) score, and Quality of Life Questionnaire Core-30 (QLQ C30) score.

Eighty subjects were randomly assigned to study drug: 41 subjects to pegcetacoplan and 39 to eculizumab. The results for the primary endpoint are presented below.

Table 2 Primary Analysis: Change From Baseline in Haemoglobin Level During the Randomised Controlled Period Using MMRM Model, Censored for Transfusion (ITT Set)

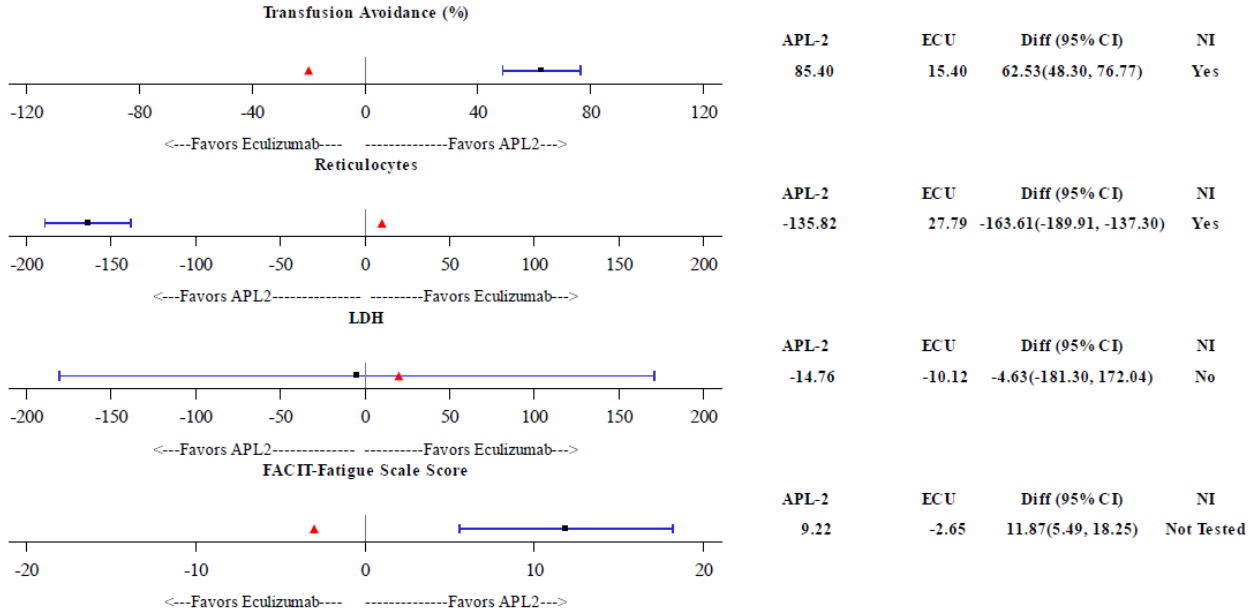
Visit	**Pegcetacoplan** **N = 41** **LS mean (SE)**	**Eculizumab** **N = 39** **LS mean (SE)**	**Difference (95% CI) in LS mean vs eculizumab**	**2-sided *P* value**
Week 2	3.07 (0.29)	0.83 (0.31)	2.24 (1.45-3.03)	<.0001
Week 4	2.78 (0.25)	−1.50 (0.30)	4.28 (3.56-5.00)	<.0001
Week 6	2.68 (0.29)	−1.51 (0.41)	4.19 (3.23-5.14)	<.0001
Week 8	2.38 (0.30)	−1.74 (0.45)	4.12 (3.07-5.18)	<.0001
Week 12	2.75 (0.29)	−1.57 (0.42)	4.33 (3.34-5.31)	<.0001
Week 16	2.37 (0.36)	−1.47 (0.67)	3.84 (2.33-5.34)	<.0001

Figure 2. LS Mean (±SE) Change From Baseline in Haemoglobin During the Randomised Controlled Period Using MMRM Model Over Time, Censored for Transfusion (ITT Set)



Transfusion avoidance was achieved by 35 of 41 subjects (85.4%) in the pegcetacoplan group and 6 of 39 subjects (15.4%) in the eculizumab group. The lower bound of the 95% CI of the 62.5% adjusted treatment difference (48.3-76.8) was greater than the prespecified NIM of –20% (nominal *P* value <.0001).

Figure 3. Plot of Noninferiority Margins and Statistics for Transfusion Avoidance, ARC, LDH Level, and FACIT-Fatigue Score During the Randomised Controlled Period (ITT Set)



Abbreviations: APL-2 = pegcetacoplan; APL2 = pegcetacoplan; ARC = absolute reticulocyte count; Diff = difference; ECU = eculizumab; FACIT = Functional Assessment of Chronic Illness Therapy; ITT = intent-to-treat; LDH = lactate dehydrogenase; NI = noninferiority.
Note: The red triangle represents noninferiority margin; the black square represents the mean

Table 3 16-Week Key Secondary Efficacy Results

Parameter	**Time point and statistics**	**Pegcetacoplan N = 41**	**Eculizumab N = 39**	**Treatment difference pegcetacoplan – eculizumab Difference (95% CI)**	**Nominal *P* value**
Transfusion avoidance	W16 (n %)	35 (85.4)	6 (15.4)	0.6253 (0.4830 to 0.7677)	<.0001
ARC (10^9/L)	Baseline (mean [SD]) CFB to W16 (LS mean [SE])	217.52 (74.96) −135.82 (6.54)	216.15 (69.14) 27.79 (11.86)	−163.61 (−189.91 to −137.30)	<.0001
LDH (U/L)	Baseline (mean [SD]) CFB to W16 (LS mean [SE])	257.48 (97.65) −14.76 (42.71)	308.64 (284.84) −10.12 (71.03)	−4.63 (−181.30 to 172.04)	.9557
FACIT-Fatigue	Baseline (mean [SD]) CFB to W16 (LS mean [SE])	32.16 (11.38) 9.22 (1.61)	31.55 (12.51) −2.65 (2.82)	11.87 (5.49 to 18.25)	.0005

In Study APL2-302, pegcetacoplan demonstrated statistically significant and clinically meaningful differences from eculizumab in efficacy outcomes in PNH patients with anaemia.

The comparative effectiveness of pegcetacoplan vs ravulizumab in PNH patients was analysed using Matching-Adjusted Indirect Comparison (MAIC) analysis. After specifying eculizumab treatment as the anchor, MAIC results show that relative to ravulizumab, pegcetacoplan is associated with statistically significant and clinically meaningful improvements across the majority of endpoints related to Hb: transfusion avoidance, transfusion requirements, IVH, fatigue, and quality of life, suggesting potential improved benefits of switching to pegcetacoplan (instead of ravulizumab) among patients previously treated with eculizumab. Despite the limitations of the MAIC analysis, the clinical and haematological endpoints examined in this MAIC are important indicators of underlying IVH and EVH. These results suggest that C3 inhibition by pegcetacoplan results in broader inhibition of complement system activation in comparison with the C5-complement inhibitor ravulizumab. This is expected because the mechanism of action of ravulizumab, which is also a C5 inhibitor, is almost identical to that of eculizumab. Accordingly, these data conclude significant benefit of pegcetacoplan for PNH patients previously treated with either eculizumab or ravulizumab.

The results show clinically important benefits of pegcetacoplan in patients not adequately controlled by eculizumab and ravulizumab, in improved Hb levels and a reduction in transfusion after 16 weeks of treatment. This supports the basis of significant benefit for the purpose of maintenance of the orphan designation.

4. COMP position adopted on 05 November 2021

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.