14 March 2024
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Voydeya ((2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide)
Treatment of paroxysmal nocturnal haemoglobinuria
EU/3/17/1946

Sponsor: Alexion Europe

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)	(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide
Other name(s)	Voydeya, (2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide,
International Non-Proprietary Name	Danicopan
Tradename	Voydeya
Orphan condition	Treatment of paroxysmal nocturnal haemoglobinuria
Sponsor's details:	Alexion Europe 103-105 Rue Anatole France 92300 Levallois Perret France
Orphan medicinal product designation procedural history	
Sponsor/applicant	FGK Representative Service GmbH
COMP opinion	31 October 2017
EC decision	12 December 2017
EC registration number	EU/3/17/1946
Post-designation procedural history	
Transfer of sponsorship	Transfer from FGK Representative Service GmbH to Alexion Europe – EC decision of 02 June 2020
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Carolina Prieto Fernandez / Robert Porszasz
Applicant	Alexion Europe
Application submission	28 February 2023
Procedure start	23 March 2023
Procedure number	EMA/H/C/005517/0000
Invented name	Voydeya
Proposed therapeutic indication	Paroxysmal nocturnal hemoglobinuria (PNH) 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/Voydeya
CHMP opinion	22 February 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Karri Penttila
Sponsor's report submission	03 April 2023
COMP opinion	14 March 2024

2. Grounds for the COMP opinion

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 (2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidine-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridine-2-yl)-4-fluoropyrrolidine-2-carboxamide was considered justified based on preliminary clinical data supporting an improvement in haemoglobin levels in patients with the condition;
- 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 approximately 0.2 in 10,000 persons in the European Union, at the time the application was made;
- In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidine-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridine-2-yl)-4-fluoropyrrolidine-2-carboxamide will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that supports a reduction in the number of transfusions needed in patients with aplastic anaemic paroxysmal nocturnal haemoglobinuria where eculizumab is not recommended. The Committee considered that this constitutes a clinically relevant advantage.

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 *"Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia (see section 5.1)."* 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 the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor concludes that PNH is a life-threatening and debilitating disease. Intravascular haemolysis and the ensuing thrombosis are the major contributor to PNH morbidity and premature mortality.

Although the standard of care treatment with Complement 5 inhibitors (C5-I) has reduced the mortality and morbidity of the disease, a small subset of patients with PNH who are treated with C5-I experience clinically significant residual haemolytic anaemia, which is thought to be partly due to extravascular haemolysis (EVH) of C3 opsonised erythrocytes, which cannot be targeted by C5-I. Despite the recent approval of pegcetacoplan, the sponsor claims that an unmet medical need remains.

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

At the time of orphan designation, the prevalence was estimated to be 0.2 in 10,000.

The sponsor has conducted a literature search to identify the most current publications. Of the four new publications that were identified in the search since the initial orphan designation in 2017, only one is from the European Union. The other three are from the UK, US and South Korea and thus are only considered supportive. The references are summarised in the table 1.

Table 1. Summary of Epidemiological Literature Reporting Prevalence of Paroxysmal Nocturnal Hemoglobinuria in the General Population

Reference	Jalbert, 2019	Hansen, 2020	Kang, 2020	Richards, 2021
Type of source	Conference abstract	Manuscript	Manuscript	Manuscript
Region/country	US	Denmark	South Korea	England
Collection year(s)	2015-2018	1980-2016	2002-2016	2004-2018
Case definition	ICD-10 code	ICD-10 code	KCD-7 code and benefiting from government healthcare and national health insurance	Flow cytometry for GPI-linked antigens on red cells, neutrophils, and/or monocytes at a single reference laboratory
Study design/ data collection method (PNH case ascertainment)	Retrospective cohort study using US administrative claims data	Retrospective cohort study using national registry data	Retrospective cohort using National Health Insurance Database	Retrospective cohort using patients diagnosed by central laboratory for the population in a single geographic area
Study population size	30 M insured patients	5.7 M patients	50.8 M insured patients	3.8 M patients
Calculated EU prevalence per 10,000	0.13	0.104 (year 2015)	0.39 (year 2016)[a]	0.38
Included in analysis	Yes	Yes	Yes	Yes Highest EU/UK prevalence estimate and applied to EU population estimates

The sponsor proposes that the prevalence is in a range from 0.1 to 0.4 in 10,000. The COMP acknowledged that few additional new publications exist which would not significantly alter the proposed range. Therefore, the initially proposed estimate of 0.2 in 10,000 was accepted.

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 there are three products authorised for this condition, these are the two C5-I Soliris (eculizumab) and Ultomiris (ravulizumab), and the Complement 3 inhibitor (C3-I) Aspaveli (pegcetacoplan).

The approved indications as reflected in the respective summaries of product characteristics (SmPC), are as follows:

Complement 5 inhibitors

"*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)".

Complement 3 inhibitor:

"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 only curative treatment for PNH is hematopoietic stem cell transplantation (HSCT) using allogeneic donors. However, given the high risks of this procedure and the possible limited availability of suitable donors, it is not taken into consideration as a satisfactory method for the Significant Benefit assessment of Voydeya.

Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) **who have residual haemolytic anaemia (see section 5.1)**. As can be read in section 5.1 of the SmPC, the indication for add-on treatment of Voydeya refers to patients on stable treatment with eculizumab or ravulizumab for at least 6 months and have haemolytic anaemia (haemoglobin [Hgb] ≤ 9.5 g/dL [5.9 mmol/L]) with absolute reticulocyte count ≥ 120 × 10^9/L. Considering this, there is an overlap with the indication of Aspaveli, and the latter product is considered a satisfactory method for the target population of Voydeya.

Significant benefit

The sponsor believes that their product will offer a clinically relevant advantage in patients who are being treated with a C5-I and continue to have residual anaemia.

The sponsor has provided data from their Phase 3 Study ALXN2040-PNH-301 which met its primary objective and all key secondary objectives, demonstrating the superiority of danicopan compared to placebo, as an add-on to background ravulizumab or eculizumab.

The study consisted of:

- Treatment Period 1 (TP1; randomized, blinded, placebo-controlled): TP1 was a head-to-head comparison between danicopan vs placebo as add-on to background ravulizumab or eculizumab under double-blind conditions for 12 weeks. Randomization (2:1) was stratified by transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening), Hgb (< 8.5 g/dL and ≥ 8.5 g/dL) at Screening, and Japanese /non-Japanese participants.
- Treatment Period 2 (TP2): At the end of Week 12, participants randomized to add-on placebo in TP1 were switched to add-on danicopan up to Week 24. Participants who were receiving add-on danicopan in TP1 continued on danicopan for an additional 12 weeks; all participants remained on their ongoing background ravulizumab or eculizumab therapy.
- Long-term Extension (LTE) Period Year 1: After completing TP2 (Week 24), participants could enter the LTE Year 1 at the same danicopan dose received at Week 24 in addition to their background ravulizumab or eculizumab therapy. The LTE allowed for continued evaluation of the durability of clinical effects and long-term safety.
- LTE Year 2: After completing LTE Year 1, participants could complete participation in this study or optionally continue to LTE Year 2.

The study population consisted of patients with PNH who experienced signs or symptoms of extravascular haemolysis (EVH) (e.g., chronic anaemia, high transfusion burden, and severe fatigue) while on stable treatment with eculizumab or ravulizumab. The study was designed to include PNH patients with clinically significant EVH, regardless of transfusion history.

The primary objective of the study was to evaluate the efficacy of danicopan as compared with placebo as add-on therapy to background ravulizumab or eculizumab therapy.

Table 2. Analysis of Primary and Key Secondary Endpoints at Week 12 – Interim Efficacy Analysis Set

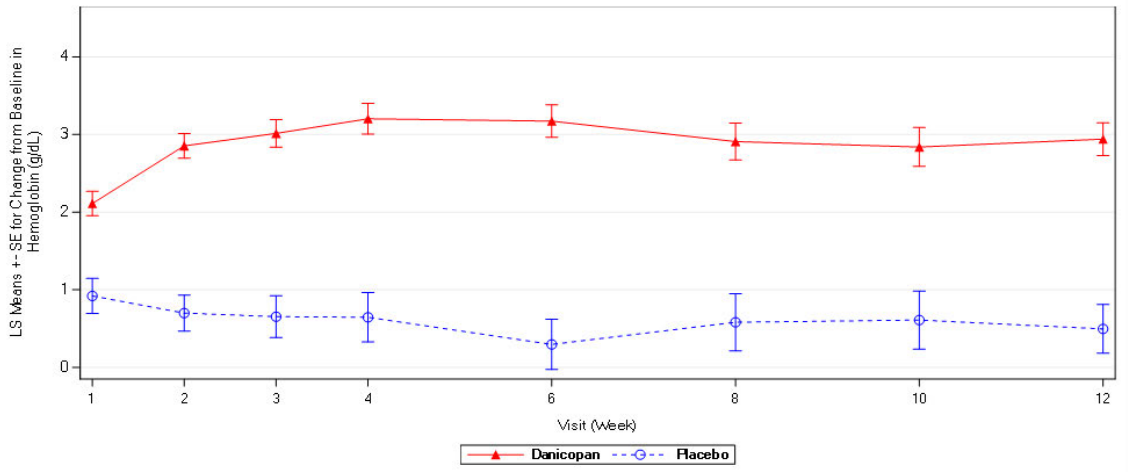
	Danicopan (Add-on with eculizumab or ravulizumab) (N = 42)	**Placebo (Add-on with eculizumab or ravulizumab) (N = 21)**
Change in hemoglobin level (primary endpoint)		
Mean change from Baseline to Week 12 (g/dL)	2.94	0.50
Treatment difference[a]	2.44 (95% CI: 1.69, 3.20)	
P-value	<0.0001	
Percentage of patients with hemoglobin increase of ≥ 2 g/dL in the absence of transfusion		
At Week 12 (%)	59.5	0
Treatment difference[b]	46.9 (95% CI: 29.2, 64.7)	
P-value	<0.0001	
Percentage of patients with transfusion avoidance		
Through 12-week treatment period (%)	83.3	38.1
Treatment difference[b]	41.7 (95% CI: 22.7, 60.8)	
P-value	0.0004	
Change in FACIT-Fatigue score		
Mean change from Baseline to Week 12	7.97	1.85
Treatment difference[a]	6.12 (95% CI: 2.33, 9.91)	
P-value	0.0021	
Change in absolute reticulocyte count ($\times 10^9$/L)		
Mean change from Baseline to Week 12	-83.8	3.5
Treatment difference[a]	-87.2 (95% CI: -117.7, -56.7)	
P-value	<0.0001	

[a] Based on MMRM test (primary analysis method under Study ALXN2040-PNH-301 Global Protocol Amendment 6.0).
[b] Difference in rates and associated 95% CI are calculated using Miettinen and Nurminen method adjusting for stratification factors as specified in the SAP.
Abbreviations: CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy; MMRM = mixed-effect model for repeated measures; SAP = statistical analysis plan
Source: ALXN2040-PNH-301 Interim CSR Tables 14.2.1.1.1, 14.2.2.1.1, 14.2.2.2.1, 14.2.2.3.1, 14.2.2.4.1

Anaemia

Add-on treatment with danicopan resulted in a statistically significant and clinically meaningful increase in Hgb from Baseline to Week 12 compared with add-on placebo (least squares [LS] mean [standard error; SE] of 2.94 [0.210] vs 0.50 [0.312] g/dL). Primary analysis using the MMRM (Mixed-Effect Model for Repeated Measures) analyses, showed statistically significant treatment effects (2.44 [0.375] g/dL Hgb; $p < 0.0001$;Figure 1 and Table 2).

Figure 1. LS Means (SE) for Change from Baseline in Hemoglobin (g/dL) through 12 Weeks – Interim Efficacy Analysis Set



Danicopan as add-on to ravulizumab or eculizumab is efficacious for the treatment of signs (low Hgb and high ARCs) or symptoms (e.g., fatigue) of residual haemolysis in adult patients with PNH. Study ALXN2040-PNH-301 met its primary objective and all key secondary objectives by demonstrating the superiority of danicopan as add-on treatment to ravulizumab or eculizumab compared with placebo as an add-on to ravulizumab or eculizumab for 12 weeks.

Based on this data the significant benefit over C5 inhibitors can be considered as established.

Significant benefit to pegcetalopan.

While pegcetacoplan (Aspaveli) targets C3 (complement 3), an abundantly present and highly variably expressed acute phase protein, danicopan targets Factor D, which is not an acute phase protein and is normally present at a concentration of 75 times lower than C3. Thus, FD as a drug target is proposed as more easily controlled than C3. It is also argued that danicopan targets the complement pathway more specifically than pegcetacoplan, which will be less likely to cause safety concerns associated with a pan-complement blocker like pegcetacoplan.

The COMP noted that significant benefit versus Aspaveli cannot be established based on differences in mechanism of action alone and should be supported by data.

Clinically relevant advantage:

The sponsor has provided a naïve indirect comparison between Study ALXN2040-PNH-301, as described above, and pegcetacoplan (Aspaveli) Phase 3 Study APL2-302.

The later study is a global, Phase 3, prospective, randomized, multicenter, open-label, active comparator-controlled study. Its objectives were to confirm treatment efficacy and safety of pegcetacoplan monotherapy for the treatment of PNH in participants aged ≥ 18 years receiving eculizumab therapy at a stable dose for at least 3 months but continue to have Hgb levels < 10.5 g/dL.

The sponsor states that the two pivotal studies APL2-302 and danicopan are not directly comparable due to the heterogeneity in study design and patient population:

- Study ALXN2040-PNH-301 is double blind, whereas Study APL2-302 is open label;
- In Study APL2-302, the comparator is eculizumab. In contrast, in Study ALXN2040-PNH-301, the efficacy and safety of danicopan as add-on treatment to background ravulizumab or eculizumab

were evaluated versus placebo. Most participants treated with danicopan in Study ALXN2040-PNH-301 were on background C5i treatment with ravulizumab (64% on ravulizumab vs 36% on eculizumab).

- In Study APL2-302, all participants were on 4 weeks of concomitant use of eculizumab and pegcetacoplan, before being randomized to either continuation of eculizumab or pegcetacoplan alone.

The inclusion criteria could be considered stricter for ALXN2040-PNH-301 than for Study APL2-302 (Table 3). Transfusion history was not an entry criterion on Study APL2-302.

Table 3. Studies APL2-302 and ALXN2040-PNH-301 Key Inclusion Criteria

	APL2-302[a]	**ALXN2040-PNH-301**	
Hemoglobin level	< 10.5 g/dL	≤ 9.5 g/dL	
Absolute reticulocyte count	> 1.0 x ULN	≥ 120 × 10^9/L	
Platelet count	> 50,000/µL	≥ 30,000/µL without the need for platelet transfusions	
Absolute neutrophil count	> 500/µL	≥ 750/µL	≥ 500/µL [b]
Transfusion history	Not required	At least 1 pRBC or whole blood transfusion within 6 months prior to the start of the study	Not required [c]

[a] Source: ASPAVELI EPAR, 2021.
[b] The absolute neutrophil count threshold for inclusion in the study was modified from 750/µL to 500/µL in ALXN2040-PNH-301 Protocol Amendment 6.0
[c] The inclusion criterion for transfusion was removed in Protocol Amendment 6; however, all participants in the Interim Efficacy Analysis Set had at least 1 pRBC transfusion 6 months prior to screening.
Abbreviations: pRBC = packed red blood cells; ULN = upper limit of normal

The sponsor has only provided a limited comparison between the two trials and has not gone into great depth regarding the comparison of the primary and secondary endpoints. What has been highlighted is that there appears to be a difference in favour of danicopan versus pegcetaloplan regarding break-through haemolysis.

The treatment effect on fatigue (FACIT-Fatigue scores) was actually lower for danicopan than for Aspaveli, in the indirect comparisons. However, in Study ALXN2040-PNH-301, FACIT-Fatigue was assessed in double-blind manner, which adds additional weight to the PRO interpretation. Add-on danicopan resulted in statistically significant and clinically meaningful improvements in mean FACIT-Fatigue scores at Week 12 compared with add-on placebo (LS mean [SE]: 7.97 [1.128] vs 1.85 [1.581]; treatment group difference: 6.12 [1.894], p = 0.0021. Improvements in FACIT-Fatigue scores were maintained over 48 weeks. In Study APL2-302, noninferiority for the FACIT-Fatigue score was not assessed due to the prespecified hierarchical testing (ASPAVELI SmPC). The unblinded nature of Study APL2-302 may have influenced the outcomes of FACIT-Fatigue scores for Aspaveli. Altogether, it is challenging to compare the outcomes for fatigue of the pivotal trial among Voydeya and Aspaveli.

Breakthrough haemolysis

A number of patients treated with pegcetacoplan experience BTH (ASPAVELI SmPC, 2022; Hillmen, 2021; Gerber, 2022; Notaro 2022) requiring discontinuation, dose adjustment and/or rescue treatment with C5i.

A summary of the TEAEs of hemolysis reported during the evaluation periods of Studies APL2-302 (Week 16 and Week 48) and ALXN2040-PNH-301 (Week 12 and Week 24) is presented in Table 4.

Table 4. Overview of Patients with TEAEs of Hemolysis Reported during the Evaluation Periods of Studies APL2-302 and ALXN2040-PNH-301

	APL2-302			**ALXN2040-PNH-301**		
	Week 16		**Week 48**	**Week 12**		**Week 24[b]**
	pegcetacoplan (N=41) n (%)	eculizumab (N=39) n (%)	pegcetacoplan (N=77) n (%)	danicopan (add-on with ravulizumab or eculizumab) (N*=49) n (%)	placebo (add-on with ravulizumab or eculizumab) (N*=24) n (%)	danicopan (add-on with ravulizumab or eculizumab) (N*=69) n (%)
AE of hemolysis	4 (9.8)	9 (23)	19 (24)	2 (4.1)	0	3 (4.3)
SAE of hemolysis	2 (4.9)	1 (2.6)	7 (9)	0	0	1 (1.4)
AE of BTH	4 (9.8)[a]	0	4 (5)[a]	0	0	2 (2.9)[a]
AE of hemolysis or BTH leading to treatment discontinuation	3 (7.3)	0	6 (8)	0	0	0

* N = number of patients treated during the treatment period
[a] Reporting of BTH differed in Studies APL2-302 and ALXN2040-PNH-301:
- APL2-302: BTH is defined as 1 new or worsening symptom or sign of intravascular hemolysis, plus a LDH level of ≥ 2 × ULN after a reduction to < 1.5 × ULN during therapy
- ALXN2040-PNH-301: BTH was not defined per protocol and hemolytic events were reported as an AE as determined by the investigator.

[b] As of the IA data cutoff 28 Jun 2022
Abbreviations: AE = adverse event; BTH = breakthrough hemolysis; LDH = lactate dehydrogenase; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Source: ASPAVELI EPAR, 2021; ASPAVELI SmPC, 2022; de Latour Supplement, 2022; Gerber, 2022; Hillmen, 2021, Ueda, 2021

The COMP noted that differences in BTH-related adverse events between both trials are difficult to interpret, as there was no correction for the different study duration, particular for the long-term extension phase (48 vs 24 weeks).

In addition, for study ALXN2040-PNH-301 (Voydeya study), no BTH/haemolytic events were reported for the placebo-group (on top of a C5 inhibitor), whereas a high number was reported for the control eculizumab arm in the Aspaveli trial. The study population in the Voydeya trial seemed to be better controlled than in the Aspaveli study. It was highlighted that the interpretation of efficacy data through adverse event reporting can be challenging.

It is understood that the indirect comparisons can be difficult, however, the claim for SB should be based on comparisons of efficacy endpoints, and not on Adverse Events (AEs), as proposed by the

sponsor. AEs are spontaneously reported and largely depend on the interpretation of the Investigator, whereas the efficacy outcomes are scored with standard validated instruments, according to a fixed and protocolised schedule.

The COMP also noted that more effort should be done to compare the primary efficacy endpoint (i.e. change from BL in haemoglobin (Hgb) levels) in both trials. It would be helpful to include some key secondary endpoints (need for transfusions, percentage of patients with Hgb Increase of ≥ 20 g/L) in the comparative analyses.

Although the Aspaveli controlled study phase was longer than for Voydeya (16 vs 12 weeks), comparison could still be made for the primary endpoint, as the 12-week data are also available for Aspaveli in the public domain (SmPC and EPAR). The fact that the Aspaveli study was open-label does not interfere with the Hgb outcomes, since these are objective laboratory results. Since the primary endpoint is a change from baseline, and in both studies patients were severely anaemic at baseline, differences in baseline Hgb values between studies are not expected to largely influence the treatment effects. The differences in control arm may neither be relevant, as these were in fact C5 inhibitors in both pivotal studies, and efficacy of ravulizumab and eculizumab have been shown to be similar (see Ultomiris EPAR).

Altogether, it is not possible to draw any conclusions on an advantage of the efficacy based on the data presented.

Major Contribution to Patient Care (MCPC):

The administration of pegcetacoplan requires frequent (2 to 3 times per week) iv infusions using 2 needles of large quantities (20 mL) of solutions. The device and refrigerated solution require a complex setup. A typical infusion time is approximately 30 minutes (if using 2 infusion sites) or approximately 60 minutes (if using 1 infusion site). The vial needs to be removed from refrigeration and kept at room temperature for at least 30 minutes. Administration of pegcetacoplan requires appropriate training in proper injection technique before self-administering. There are 10 steps that the patient needs to follow each time an infusion is administered (ASPAVELI SmPC, 2022). In Study APL2-302, 37% patients in the pegcetacoplan group reported injection-site reactions (vs 3% in the eculizumab group) (Hillmen, 2021).

As the half-life of pegcetacoplan is short (8 days), plasma levels may decrease below the efficacy threshold with missed doses or device-related issues (ASPAVELI SmPC, 2022; Notaro, 2022) not maintaining sufficient efficacy to address IVH and its life-threatening consequences.

Danicopan is an oral medication administered tid as an add-on to C5 inhibitors which are administered intravenously (IV) every 8 weeks for ravulizumab, and every 2 weeks for eculizumab. Missed doses are expected to have no impact on IVH control since patients are on background C5 inhibition.

Supporting data from a survey has been submitted to support the claim of MCPC based on patient preference. A double blinded patient survey was conducted in 29 patients with PNH between Dec 2020 and Jan 2021 comparing pegcetalopan to danicopan regarding medicinal administration.

The administration of danicopan add-on to ravulizumab (described as: "oral pill three times daily in addition to every 8-week [nurse-administered] intravenous (IV) infusion") was concluded to be relatively more desirable versus pegcetacoplan (described as: "self-administered infusion 2-3 times per week.")

Thirty-one percent of patients surveyed included the danicopan regimen among their top 3 desirable routes of administration/frequency, whereas none of the patients included the pegcetacoplan regimen

(data on file). Of note, the product names were not shown to respondents in the survey, but only the route of administration/frequency. Although pegcetacoplan is administered as a monotherapy; its route and frequency of administration are not perceived as more desirable by patients.

The COMP noted that the sponsor has provided a very limited information and details regarding a patient survey and more information should be provided in order for the COMP to assess the strengths and weaknesses of the survey. It is unclear which treatment the patients had actually received. If indeed the survey described pegcetaloplan as an infusion this would qualify as a significant bias in favour of the sponsor product. It is neither clear from the data presented, how the eculizumab based regimen (requiring IV infusion every 2 weeks) was rated. Not all PNH patients are eligible for less frequently dosed ravulizumab, because of re-imbursement issues.

Of note is that for a claim of MCPC, at least comparable efficacy and safety should be established versus the satisfactory treatment, Aspaveli.

COMP discussion following the list of questions

The sponsor considered it challenging to compare the treatment effects of Voydeya on the primary endpoint in indirect comparisons versus Aspaveli including:

- Important differences between the design of Studies ALXN2040-PNH-301 and APL2-302 (blinded vs open-label, different study duration, inclusion criteria)
- The study population in Study ALXN2040-PNH-301 that is better controlled than in Study APL-302 (explained by the add-on treatment with eculizumab and ravulizumab in Study ALXN2040-PNH-301) and,
- The underperformance of the eculizumab group in Study APL-302, as acknowledged in the Aspaveli EPAR.

Table 5. Side-by-side presentation of Voydeya (Study ALXN2040-PNH-301) and Aspaveli (Study APL2-302) Week 12 data

Endpoints	**Week 12**	
	Voydeya N = 42	**Aspaveli** N = 41
Hgb (g/dL) change from baseline LS mean (SE)	2.94 (0.210)	2.75 (0.285)
Percentage of patients with transfusion avoidance	83.3	85.4*
FACIT-Fatigue scores change from baseline LS mean (SE)	7.97 (1.128)	10.02 (1.328)
LDH change from baseline (U/L) LS mean (SE)	-23.49 (8.287)	-11.11 (51.257)

The COMP considered that based on these high-level unmatched comparisons, no conclusions can be drawn regarding an advantage of efficacy of Voydeya over Aspaveli.

The main focus of the sponsor is on the safety aspects and the claim that patients treated with Aspaveli monotherapy are more prone to BTH while this it unlikely to happen with Voydeya which is an add-on therapy.

The sponsor claims that data from Study ALXN2040-PNH-301 demonstrated the well-controlled IVH in patients with PNH treated with danicopan add-on to eculizumab and ravulizumab, as opposed to Aspaveli, as summarised in the tables below.

The Sponsor provided a new post-hoc analysis for the BTH cases, and only BTH events with LDH > 2 x ULN (i.e. lactate dehydrogenase levels above two times the upper level of normality) are presented in the table. LDH is an acknowledged biomarker of IVH. Of the, in total, six cases of BTH that were reported by investigators in the pooled data set of the danicopan add-on studies, only one case was assigned post-hoc as a BTH case. In the remaining 5 cases, the LDH levels remain below the critical threshold of LDH > 2 x ULN.

Table 6. Overview of BTH reported in Studies ALXN2040-PNH-301, APL2-302, ALXN1210-PNH-301 and ALXN1210-PNH-302

	APL2-302			ALXN2040-PNH-301				ALXN1210-PNH-301	ALXN1210-PNH-302
	Week 16	Week 48	Over 3 years	Week 12 (TP1)	Week 24 (TP2)		Up to data cut-off (31 Mar 2023)[b]	Up to 6 years	Up to 4 years
	Peg (N = 41) n (%)	Peg (N = 77) n (%)	Peg (N = 80) n (%)	Dan (N = 57) n (%)	Dan/Dan (N = 55) n (%)	Pbo/Dan (N = 27) n (%)	Total (N = 84) n (%)	Ravulizumab Total (N = 244) n (%)	Ravulizumab Total (N = 192) n (%)
AE of BTH[a]	4 (9.8)	18 (23.4)	23 (28.8)	0	0	0	1 (1.2)	36 (14.8)	15 (7.8)
AE of BTH leading to treatment discontinuation	3 (7.3)	6 (7.8)	Not available	0	0	0	0	0	0

[a] Reporting of BTH differed in Studies APL2-302 and ALXN2040-PNH-301:
- APL2-302: BTH is defined as 1 new or worsening symptom or sign of intravascular haemolysis, plus a LDH level of ≥ 2 × ULN after a reduction to < 1.5 × ULN during therapy
- ALXN2040-PNH-301: BTH was not defined per protocol and haemolytic events were reported as an AE as determined by the investigator. BTH events with LDH >2 x ULN are presented in the table.

[b] The overall mean (range) exposure to danicopan during the entire study through the data cutoff date of 31 Mar 2023 was 426.4 (44.0 to 769.0) days or 60.9 (6.3 to 109.9) weeks.

Abbreviations: AE = adverse event; BTH = breakthrough haemolysis; Dan = danicopan; LDH = lactate dehydrogenase; Pbo = Placebo; TP = Treatment Period

Source: APL2-302: de Latour, 2022; Hillmen, 2021; de Castro, 2023; ALXN2040-PNH-301: Data cutoff 31Mar2023 ALXN2040-PNH-301 Tables 14.3.1.3.2.2.1, 14.3.1.3.2.2.2, and 14.3.1.3.2.2.3; ALXN1210-PNH-301 and ALXN1210-PNH-302: data on file

Table 7 Breakthrough events reported in pegcetacoplan- and danicopan-treated patients

Study	Duration of treatment	Patients with BTH	LDH during BTH (U/L) (x ULN)	Hgb during BTH (g/dL)	Day of occurrence	Actions taken
PEGCETACOPLAN						

Table 7 Breakthrough events reported in pegcetacoplan- and danicopan-treated patients

Study	Duration of treatment	Patients with BTH	LDH during BTH (U/L) (x ULN)	Hgb during BTH (g/dL)	Day of occurrence	Actions taken
APL2-302[1-4]	16-week	9.8% (4/41) *4 BTH events*	1539-2481 (6.8 - 11.0)	10.9-6.4	D42-47 D47-53	Pegcetacoplan treatment was discontinued, and patient switched back to eculizumab
			1100-813 (4.9 - 3.6)	8.5-7.2	D49-56	Pegcetacoplan treatment was discontinued, and patient switched back to eculizumab
			4147 (18.3)	7.2-4.8	D36-39	Pegcetacoplan treatment was discontinued, and patient switched back to eculizumab
			3015-2423 (13.3 - 10.7)	6-8.3	D106-140	No action, patient remained in trial
	48-week	23.4% (18/77)[b]	790-222 (3.5 - 0.98)	8.6-11.6	D197-322 (OLP)	Pegcetacoplan treatment was discontinued
			460-840 (2.0 - 3.7)	7.3-8.9	D192-199 (OLP) D275-283 (OLP)	Pegcetacoplan treatment was discontinued
			189 (N/A)	14.2	D329-349 (OLP)	Pegcetacoplan treatment was discontinued
	3-year	28.8% (23/80)	Not available	Not available	Not available	Not available
Acute BTH[a,5]	OLE (after 48 weeks in APL2-302, 26 weeks in APL2-308, or 52 weeks in 204)	9.5% (13/137)[c] *17 BTH events*	> 1000 – 10000 in 11/13 patients	Males: 7/8 < LLN (13 g/dL) Females: 5/5 < LLN (12 g/dL)	N/A	Intensive off-label pegcetacoplan IV or SC dosing (all patients) Eculizumab initiation as add-on to pegcetacoplan (1 patient)
RWE[6]	Mean pegcetacoplan exposure: 20.2 months	12.5% (6/48) *18 BTH events*	5.4 x ULN (range 1.8-13.2)	2.2 g/dL drop (range 0-6.9 g/dL)	N/A	Transfusion: 10 events 3 days pegcetacoplan SC: 9 events Eculizumab initiation or dose increase: 8 events No changes: 3 events

Table 7 Breakthrough events reported in pegcetacoplan- and danicopan-treated patients

Study	Duration of treatment	Patients with BTH	LDH during BTH (U/L) (x ULN)	Hgb during BTH (g/dL)	Day of occurrence	Actions taken
DANICOPAN						
ALXN2040-PNH-301[d]	12-week	0	N/A	N/A	N/A	N/A
	24-week	0	N/A	N/A	N/A	N/A
	LTE (up to 2 years)	1.3% (1/80) *1 BTH event*	632 (2.2)	9.2 g/dL	D192	Recovered
ACH471-101[d]	LTE (up to 4 years)	*8.3% (1/12)* *1 BTH event*	900 (3.6)	6.0 g/dL	D948	Recovered Transfusions, loading dose of eculizumab

[a] Acute BTH defined by lactate dehydrogenase (LDH) > 2 x upper limit of normal (ULN) and the presence of at least 1 new or worsening sign or symptom of haemolysis (e.g., decreased Hgb, haemoglobinuria, fatigue, etc.), that in the opinion of the investigator warrants an acute intervention.
[b] Narratives only available for 3 out of 18 patients
[c] These 13 patients include 10 patients from APL2-302, 2 from APL2-308 and 1 from 204
[d] BTH events with LDH >2 x ULN are presented in the table.
Abbreviations: BTH = breakthrough haemolysis; Hgb = haemoglobin; IV = intravenous; LDH = lactate dehydrogenase; LTE = long-term extension; N/A = not applicable; OLE = open-label extension; OLP = open-label phase; RWE = real-world evidence; SC = subcutaneous
Source: Pegcetacoplan: 1 = Hillmen, 2021; 2 = Kulasekararaj 2021; 3 = de Latour, 2022; 4 = de Castro, 2023; 5 = Griffin, 2024a; 6 = Griffin, 2024b; Danicopan: Data cutoff 31Mar2023 ALXN2040-PNH-301 Tables 14.3.1.3.2.2.1, 14.3.1.3.2.2.2, and 14.3.1.3.2.2.3, Listing 16.2.8.2.4, and ACH471-101 Interim CSR Narratives

The sponsor also submitted an Expert statement and the expert confirms the Sponsor's concern with patients on Aspaveli being at risk of BTH:

- There are patient groups for whom pegcetacoplan is not a sufficient or long-term applicable therapy.
- The experience since its approval of pegcetacoplan (Aspaveli®) in Germany shows that subcutaneous infusions are not preferred by many patients and that the need for storage at +2oC to +8oC and the need for the infusion pump and consumables is a major restriction, especially when traveling (Note COMP: *but MCPC claim is not sought by the Sponsor anymore*).
- The severity of BTH in some patients on pegcetacoplan can even resemble the intravascular haemolysis in untreated PNH patients. Based on experience, also full reversion to C5 inhibitor treatment can become necessary.
- It has been suggested that a combined approach, i.e. inhibition of both proximal and terminal pathway, may be the best option by preventing C3 binding to PNH erythrocytes and thus EVH, in addition to preventing massive BTH and at the same time maintaining the benefit of terminal complement inhibition (Notaro 2022).
- BTH events are clinically meaningful since they put the patients at risk of PNH complications. Therefore, the frequency, severity and duration of these events must be minimized as much as possible.

It is recognised that although BTH is an unwanted adverse effect and was presented as a safety outcome in the registration dossier, it can also be used as a measure of efficacy. The sponsor indicated that approximately 10-20% of C5 inhibitor-treated patients who have achieved durable IVH control may experience emergence of extravascular haemolysis (EVH) and could be considered to be a more severe PNH patient population. The COMP noted that this occurred in patients who had LDH above the ULN. The sponsor argued that there were more patients with BTH in the placebo group. The increase in more BTH in this group could be linked to the placebo arm underperforming due to the trial design and a possible rebound effect.

Danicopan as add-on was developed for the treatment of signs or symptoms of EVH while maintaining a durable IVH control with eculizumab or ravulizumab. This target patient population is not treated with a C3 inhibitor which is generally given as a substitution for a C5 inhibitor associated with breakthrough haemolysis. Actually, in the SmPC of Aspaveli it is recommended to discontinue the previous C5 inhibitors. Although combined use is not contra-indicated, there is no data presented and neither a specific recommendation to use Aspaveli in combination treatment with a C5 inhibitor, as a rescue treatment in case of a BTH in the SmPC or EPAR (European Assessment Report) of this product.

The sponsor argued that they identified a target patient population where there was a risk of either BTH or IVH when they were treated with Aspaveli as there were more breakthrough haemolysis events compared with the group where danicopan was used in combination with a C5 inhibitor. It was concluded that combination treatment offered better protection against to BTH which could be associated with a higher risk of IVH in these more severe patients.

COMP Conclusions

The COMP accepted that this target patient population represented an at-risk patient population which could not be adequately treated with Aspaveli when used in substitution of a C5 inhibitor. Severe BTH has been reported for Aspaveli in a clinically relevant percentage of the treated population. The possibility to control patients with PNH without causing severe BTH is considered a clinically relevant

advantage. This represented a clinically relevant advantage which would support significant benefit. As a clinically relevant advantage had been established there was no need to establish a major contribution to patient care.

The Committee therefore agreed to recommend maintaining the orphan designation.

4. COMP position adopted on 14 March 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 0.2 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 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;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by the therapeutic indication of Voydeya, the claim that Voydeya is of significant benefit to those with the subset of the orphan condition as defined in the granted therapeutic indication is established. The sponsor has submitted clinical data which showed that combination treatment with Voydeya and a complement 5 inhibitor offers a clinically relevant advantage (fewer breakthrough haemolysis) in patients with residual haemolytic anaemia who are at risk of severe intravascular haemolysis compared to Aspaveli, a complement 3 inhibitor.

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 Voydeya, (2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide, danicopan for treatment of paroxysmal nocturnal haemoglobinuria (EU/3/17/1946) is not removed from the Community Register of Orphan Medicinal Products.