

# Safety and efficacy of pegcetacoplan in paroxysmal nocturnal hemoglobinuria

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*Ther Adv Hematol*

2022, Vol. 13: 1–17

DOI: 10.1177/  
20406207221114673

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**Abstract:** Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, hematologic disease characterized by complement-mediated hemolysis, thrombosis, and various degrees of bone marrow dysfunction. Until recently, C5 inhibition with eculizumab or ravulizumab represented the only therapies approved for patients with PNH by the United States Food and Drug Administration (US FDA). Although C5-inhibitors reduce PNH-related signs and symptoms, many patients continue to exhibit persistent anemia and require frequent blood transfusions. In May 2021, pegcetacoplan became the third US FDA-approved treatment for adults with PNH, and the first to target C3, a complement component upstream of C5. The novel strategy of inhibiting proximal complement activity with pegcetacoplan controls C5-mediated intravascular hemolysis and prevents C3-mediated extravascular hemolysis. Here, we review the results from multiple pegcetacoplan clinical studies on the efficacy and safety of pegcetacoplan treatment in adults with PNH. This review summarizes findings from three studies in complement-inhibitor-naïve patients with PNH (PADDOCK [phase Ib], PALOMINO [phase IIa], PRINCE [phase III; pegcetacoplan versus standard treatment excluding complement-inhibitors]), and one phase III study (PEGASUS) that compared eculizumab to pegcetacoplan in patients who remained anemic (hemoglobin levels < 10.5 g/dL) despite stable eculizumab treatment (≥3 months). These studies found that pegcetacoplan contributed to superior improvements in primary and secondary endpoints related to hemoglobin levels and other hematologic parameters and provided effective management of anemia and anemia-related complications (i.e. transfusion burden, reticulocyte production, and fatigue). Furthermore, we summarize results from the 32-week open-label period from the PEGASUS trial, which confirmed the long-term safety and durable efficacy of pegcetacoplan as demonstrated by sustained improvements in clinical and hematologic outcomes in pegcetacoplan-treated patients. Pegcetacoplan is approved for the treatment of adults with PNH in the United States (Empaveli™) and for adult patients who remain anemic after at least 3 months of stable C5-inhibitor therapy in the European Union (Aspaveli®) and Australia (Empaveli; also approved for patients intolerant to C5-inhibitors).

**Keywords:** anemia, complement-inhibitor, hemolysis, paroxysmal nocturnal hemoglobinuria, pegcetacoplan, quality-of-life

Received: 15 January 2022; revised manuscript accepted: 4 July 2022.

## Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, hematologic disease characterized by complement-mediated hemolysis,

thrombosis, and mild-to-severe bone marrow dysfunction.<sup>1</sup> While its global prevalence is understudied,<sup>2</sup> PNH has been estimated to affect as many as 16 individuals per million worldwide.<sup>3,4</sup>

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A 2020 analysis of data from the International PNH Registry – a worldwide, observational, non-interventional repository of safety, efficacy, and quality-of-life (QoL) data from patients with confirmed PNH – revealed that the median age at disease onset is 35.5 years old.<sup>5</sup> Prior to the development of eculizumab, and later ravulizumab, to inhibit terminal complement activation with C5 blockade, there were no United States Food and Drug Administration (US FDA)-approved therapies for PNH. Although C5-inhibitor (C5i) therapy has improved outcomes for patients with PNH,<sup>6–9</sup> many C5i-treated patients experience residual complement-mediated hemolysis, unresolved anemia, and anemia-related complications (i.e. transfusion burden, fatigue, and impaired QoL).<sup>10–12</sup>

Pegcetacoplan is the first C3-targeted complement-inhibitor that was approved for the treatment of adults with PNH by the US FDA (May 2021)<sup>13</sup> and for adults who remain anemic despite stable treatment with C5i for at least 3 months by the European Medicines Agency (EMA, December 2021)<sup>14</sup> and the Australian Therapeutic Goods Agency (February 2022; also approved for patients intolerant to C5i).<sup>15</sup> Pegcetacoplan provides a novel approach for preventing complement-mediated hemolysis by targeting the proximal complement protein C3, a component that is upstream of C5. Thus, C3 inhibition with pegcetacoplan can provide control over both proximal and terminal complement activation and prevent extravascular and intravascular hemolysis, respectively. Here we review the results from several early and late phase clinical studies conducted to assess the safety and efficacy of pegcetacoplan in complement-inhibitor-naïve patients with PNH and in an active-comparator study with eculizumab among patients who remained anemic despite stable eculizumab treatment. We also provide a brief overview of the pathophysiology and clinical manifestations of PNH, and background information on C5-inhibiting therapies for PNH.

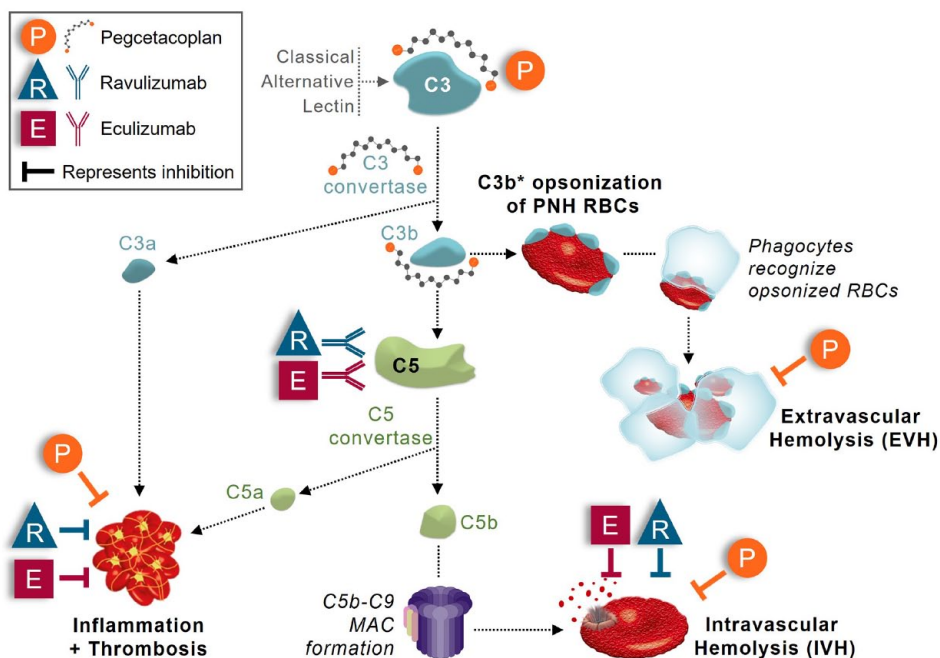
### **An overview of PNH pathophysiology**

PNH is caused by somatic mutations in the X-linked phosphatidylinositol glycan class A (*PIGA*) gene locus of hematopoietic stem cells.<sup>16,17</sup> *PIGA* encodes one of the several proteins involved

in the first step of glycosylphosphatidylinositol (GPI) anchor biosynthesis.<sup>16,18</sup> While a number of *PIGA* mutations have been observed in patients with PNH, most are located in exon 2 of the gene and result in the severe deficiency or absence of GPI anchors.<sup>19</sup> GPI anchors integrate more than 20 different proteins, including the complement-inhibitor proteins CD55 and CD59, in the membrane of hematopoietic cells, resulting in their expression at the cell surface.<sup>20</sup>

CD55 and CD59 cell surface expression protects red blood cells (RBCs) from lysis mediated by distinct complement molecules and the membrane attack complex (MAC). CD55, or ‘decay-accelerating factor’, regulates the proximal complement cascade by preventing the formation of membrane-bound C3 convertase, accelerating C3 convertase decay, and ultimately inhibiting the conversion of C3 into C3b and C3a.<sup>21,22</sup> CD59 prevents terminal complement activity by blocking the aggregation of C9 with other component molecules (C5b, C6, C7, C8) necessary for MAC formation, thereby preventing intravascular hemolysis.<sup>22,23</sup> Deficiency or absence of CD55 and CD59 thus results in chronic complement-mediated hemolysis in patients with PNH, and a greater than 90% reduction in the lifespan of PNH RBCs as compared to normal RBCs.<sup>24</sup>

Complement can be activated through multiple pathways (i.e. classical, alternative, and lectin) that converge at the complement component C3, which is the central protein in the complement cascade.<sup>25</sup> C3 is cleaved into the anaphylatoxin, C3a, and the opsonin, C3b. C3b plays a central role in complement-mediated hemolysis in PNH by contributing to the opsonization of clonal RBCs (by C3b and its degradation products)<sup>25</sup> leading to extravascular hemolysis and to the formation of C5 convertase, leading to C5b generation, MAC formation, and intravascular hemolysis (Figure 1).<sup>22</sup> The chronic hemolysis associated with PNH manifests distinctly depending on whether it is due to intravascular or extravascular hemolysis. Intravascular hemolysis presents clinically as decreased hemoglobin levels, increased serum levels of lactate dehydrogenase ([LDH] an enzyme released from lysed RBCs) and bilirubin (product of heme catabolism), and an elevated absolute reticulocyte count



**Figure 1.** The complement cascade and complement-inhibitors approved by the US FDA, EMA, and Australian Therapeutic Goods Agency for the treatment of PNH [Pegcetacoplan (P); Eculizumab (E); and Ravulizumab (R)]. By inhibiting C3 and C3b, pegcetacoplan exerts broad inhibition of the complement cascade, reduces the risk of thrombosis, and prevents both intravascular hemolysis and extravascular hemolysis. C5-inhibitors eculizumab and ravulizumab can reduce thrombosis and intravascular hemolysis but do not address extravascular hemolysis.

EVH, extravascular hemolysis; IVH, intravascular hemolysis; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria; RBCs, red blood cells.

\*PNH RBCs can become opsonized by C3b and its degradation products, iC3b and C3dg, which target PNH RBCs for the destruction by phagocytosis/extravascular hemolysis in the liver and spleen.<sup>25</sup> The relative role of C3b, iC3b, and C3dg in promoting extravascular clearance of PNH RBCs is still under investigation.

(ARC) due to the bone marrow's compensatory production of RBCs.<sup>1,26</sup> Residual intravascular hemolysis in patients receiving C5i therapy may occur for several reasons, including pharmacokinetic breakthrough (e.g. due to insufficient C5i dosing), pharmacodynamic breakthrough (i.e. complement activation in the setting of a complement-amplifying condition), or rare C5 genetic polymorphisms.<sup>27</sup> C3-mediated extravascular hemolysis can occur in patients with PNH despite C5i therapy and has a slightly different clinical presentation in which levels of bilirubin and ARC, but not necessarily LDH, are increased.<sup>28–31</sup>

### Clinical manifestations of PNH

The classification of PNH proposed by the International PNH Interest Group includes three

subtypes:<sup>32</sup> (1) classical PNH, which includes hemolytic and thrombotic patients who have evidence of PNH in the absence of another bone marrow failure disorder; (2) PNH in the context of other primary bone marrow disorders, such as aplastic anemia or myelodysplastic syndrome; and (3) subclinical PNH, in which patients have small PNH clones but no clinical or laboratory evidence of hemolysis or thrombosis. These subtypes are associated with different implications for the QoL of patients with PNH. While patients with subclinical PNH may lead normal lives, patients with clinically significant disease experience signs and symptoms of PNH that can be debilitating and impact their QoL.

The symptomatology of patients with PNH is well-documented in the International PNH Registry.<sup>5</sup> Substantial proportions of enrolled

patients exhibited a history of physician-reported PNH-related symptoms at baseline; fatigue was the most common (80.0%), while other symptoms included dyspnea (45.3%), hemoglobinuria (45.0%), abdominal pain (35.2%), dysphagia (16.5%), and erectile dysfunction (24.2% of male registrants).<sup>5</sup> In the overall population of patients with PNH, patient-reported scores from QoL assessments based on the psychometrically validated Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health/QoL scales demonstrated impaired QoL and considerable fatigue, with median scores of 34.0 and 58.3, respectively.<sup>5</sup> Normative mean reference scores for the general adult population have been reported on the FACIT-Fatigue (43.6)<sup>33</sup> and EORTC QLQ-C30 global health/QoL (75.7)<sup>34</sup> scales, with a  $\geq 3$ -point decrease in FACIT-Fatigue scores<sup>35</sup> and  $\geq 10$ -point decrease in EORTC QLQ-C30 global health/QoL scores<sup>36,37</sup> considered clinically meaningful.

#### **C5-inhibiting therapies for PNH and unmet needs**

Prior to the development of complement-inhibitors, there were no US FDA-approved therapies for patients with PNH. Clinical management of PNH was primarily supportive, with a median survival after diagnosis of approximately 10 years for patients with clinically significant PNH.<sup>38</sup> Most PNH-related deaths were due to thrombotic events.<sup>38,39</sup>

The C5i, eculizumab (a monoclonal antibody reactive against C5; Alexion Pharmaceuticals, Inc.), was the first therapy to be US FDA-approved for treatment of patients with PNH in March 2007. Phase II/III clinical trials of eculizumab in patients with PNH demonstrated its long-term efficacy and safety, with results showing sustained improvements in hemolytic markers, such as LDH, hemoglobinuria, and transfusion requirements, and patient-reported QoL measures.<sup>40,41</sup> These trials also showed lower rates of life-threatening thrombotic events and survival comparable to that of age- and sex-matched controls without PNH.<sup>42</sup> There are, however, several clinical and

practical limitations to eculizumab therapy. The indefinite 2-week intravenous dosing schedule due to the drug's short half-life (one reason for eculizumab's high cost of therapy) can be inconvenient for patients by increasing the frequency of infusion clinic visits.<sup>40</sup> Many patients also require doses higher than those approved for PNH, with nearly half of all patients in a recent study receiving higher than the label-recommended 900 mg biweekly maintenance dose.<sup>43</sup> These findings are of particular concern due to the demonstrated temporal association with eculizumab dosing, suboptimal C5 inhibition, and breakthrough hemolysis.<sup>44</sup>

US FDA approval of the next therapy for patients with PNH, the C5i ravulizumab (Alexion Pharmaceuticals, Inc.), did not occur until December 2018. Ravulizumab is derived from the same antibody clone as eculizumab, but features amino acid substitutions that extend its half-life.<sup>45</sup> Ravulizumab provides patients with therapeutic benefits similar to those of eculizumab while reducing the incidence of breakthrough hemolysis events<sup>8,9,44</sup> and enabling a more convenient 8-week dosing schedule compared to eculizumab.<sup>40</sup> Phase III trial data demonstrated similar safety profiles for ravulizumab and eculizumab,<sup>8,9</sup> yet ravulizumab did not provide a novel mechanism for inhibiting complement-mediated hemolysis, resulting in a C5i therapy for PNH that shared many limitations with its predecessor.

While C5i therapies have improved the clinical management of PNH, there are several limitations associated with the use of these treatments. A considerable proportion of patients treated with C5i therapy continue to exhibit signs and symptoms of ongoing hemolysis.<sup>10,46</sup> Persistent anemia may occur in C5i-treated patients with PNH due to comorbidities associated with bone marrow failure (i.e. aplastic anemia and myelodysplastic syndromes).<sup>47,48</sup> Studies have also suggested that ongoing hemolysis may occur in C5i-treated patients due to C5i unmasking a low-level of additional extravascular hemolysis in patients with PNH. It has been suggested that this additional low-level extravascular hemolysis occurs when PNH RBCs are not destroyed by intravascular hemolysis in the presence of C5i, leaving these excess PNH RBCs susceptible to C3b

opsonization and extravascular hemolysis.<sup>28–30,46,49</sup> In addition, residual intravascular hemolysis in the presence of sufficient C5i dosing can occur for a number of reasons including (1) the presence of complement-amplifying conditions, such as major surgery, infection, or third trimester pregnancy;<sup>50</sup> (2) existing comorbidities, such as atypical hemolytic uremic syndrome (aHUS);<sup>51</sup> or (3) evasion of C5i through a C3 bypass mechanism.<sup>52</sup> The C3 bypass mechanism occurs with dense C3b opsonization on RBCs that induces a C5b-like conformation in C5 leading to C5 convertase-independent MAC formation.<sup>52</sup> This bypass mechanism further highlights the need for pharmacotherapies for PNH that directly inhibit C3b opsonins.

Major concerns with ongoing hemolysis with C5i therapies are related to the consequences of persistently low hemoglobin levels/anemia and chronic transfusion dependence. Many patients with PNH receiving C5i therapy fail to achieve hemoglobin normalization with hemoglobin levels above the lower limit of normal (LLN).<sup>10–12</sup> Persistently low hemoglobin levels and unresolved anemia can result in multi-organ damage due to reduced blood oxygen capacity<sup>53</sup> and contribute to fatigue and impairments in QoL.<sup>10,54</sup> More than 75% of C5i-treated patients with PNH report unresolved fatigue, and many patients report impairments in overall QoL, decreased productivity, and activity impairment. Relatedly, persistent anemia can also lead to chronic transfusion dependence, which is associated with complications such as iron overload.<sup>55</sup> Notably, more than half of the patients with PNH receiving C5i therapy report ongoing transfusion requirements.<sup>10</sup>

Additional concerns regarding the clinical utility of C5i therapies include hepatotoxicity and the development of bilirubin gallstones with long-term use. Although further pharmacovigilance research is required to evaluate hepatotoxicity in C5i-treated patients with PNH, hepatotoxicity has been observed among some aHUS patients treated with eculizumab who displayed elevated liver enzyme levels following eculizumab treatment.<sup>56,57</sup> Furthermore, increased bilirubin levels due to unresolved extravascular hemolysis in C5i-treated patients with PNH can increase the likelihood of developing bilirubin gallstones.<sup>58</sup>

### The development of pegcetacoplan

The inability of C5i treatment to thoroughly control intravascular hemolysis and prevent extravascular hemolysis in patients with PNH has driven the development of pharmacotherapies that target alternative molecules in the complement cascade, such as C3 with pegcetacoplan.<sup>59</sup> Research on C3 as a possible therapeutic target has been conducted over the past several decades and is punctuated by the development of the first peptidic C3-inhibitor, compstatin.<sup>60–62</sup> Pegcetacoplan (Empaveli™/Aspaveli®; FDA/EMA), a PEGylated and bivalent variation of a second-generation compstatin analog, was developed and validated by Apellis Pharmaceuticals, Inc. Pegcetacoplan consists of two 15-amino acid cyclic peptides conjugated to a linear polyethylene glycol molecule to increase its half-life.

Pegcetacoplan prevents downstream C3 activity by binding C3 and its cleavage product, C3b; thus inhibiting C3 activation by its convertase, C3b opsonization of RBCs, and C3b's role in the downstream activation of C5 by its convertase (Figure 1).<sup>63–65</sup> As pegcetacoplan targets the complement cascade upstream of C5 (targeted by ravulizumab and eculizumab), it provides more complete hemolysis protection by reducing terminal complement-mediated intravascular hemolysis and preventing C3b-associated extravascular hemolysis (Figure 1).<sup>13,64,66</sup> Comprehensive control of complement-mediated hemolysis with pegcetacoplan enables substantial improvements in key PNH outcomes including improvements in hematologic parameters (hemoglobin, LDH, ARC, bilirubin) and anemia-related complications (transfusion requirements, fatigue, and QoL). These data are discussed in the following section, which presents results from multiple pegcetacoplan clinical studies among complement-inhibitor-naïve patients and patients who demonstrated insufficient response to stable eculizumab treatment.

### The safety and efficacy of pegcetacoplan in clinical trials

#### PHAROAH

PHAROAH (NCT02264639) was a phase Ib, open-label, prospective, non-randomized, single and multiple ascending dose trial conducted

across seven clinical sites in the United States.<sup>64,67</sup> Key eligibility criteria included patients with PNH aged  $\geq 18$  years, weighing  $> 55$  kg, with a hemoglobin level  $< 10$  g/dL despite  $\geq 3$  months of treatment with eculizumab.<sup>64</sup> The trial consisted of four cohorts, with patients being able to participate in multiple cohorts.<sup>64</sup> Initially, pegcetacoplan (25–360 mg/day dosing range depending on the cohort) was administered subcutaneously by trained research personnel.<sup>64</sup> Patients transitioned to self-administered subcutaneous pegcetacoplan infusion following the introduction of an ambulatory syringe pump and were required to continue their regular eculizumab dosing regimen throughout the trial;<sup>64</sup> A total of nine patients were enrolled in the trial; four patients completed the 2-year trial; enrolled in the extension study, and discontinued eculizumab between Day 457 and Day 626.<sup>64</sup>

The PHAROAH trial's primary endpoints were the number and severity of treatment-emergent adverse events (TEAEs) and pegcetacoplan pharmacokinetic parameters.<sup>64,67</sup> Overall, 427 TEAEs were reported over the 2-year trial period: 68 TEAEs were considered possibly related to pegcetacoplan, with 48 of these TEAEs related to the drug injection site.<sup>64</sup> Twelve serious adverse events (SAEs) were reported in two patients (of which eight were TEAEs). Steady-state serum concentration of pegcetacoplan was reached in most patients approximately 6–8 weeks after dosing initiation, although some patients may have reached steady-state serum concentration between 4 and 6 weeks.<sup>64</sup>

Pegcetacoplan treatment in PHAROAH increased hemoglobin levels (at the 2-year timepoint, three of four patients exhibited hemoglobin levels within the normal range of 11.1–15.9 g/dL) and reduced ARC, LDH, and total bilirubin. The majority of PHAROAH patients (three of four) demonstrated a clinically meaningful change of a  $\geq 3$ -point<sup>35</sup> improvement in score on the FACIT-Fatigue scale.<sup>64</sup> Transfusion avoidance was achieved in all patients who completed the study.<sup>64</sup> In addition, pegcetacoplan increased the clonal distribution of type II and III PNH RBCs and decreased C3 fragment deposition on the surface of these cells.<sup>64</sup>

Overall, the PHAROAH trial demonstrated that treatment with pegcetacoplan was generally well-tolerated and improved hematological outcomes by achieving broad control of hemolysis through C3 inhibition in a small patient population that was initially receiving eculizumab.

#### *PADDOCK and PALOMINO*

Two open-label trials were initiated to investigate whether complement-inhibitor-naïve patients with PNH could equally benefit from pegcetacoplan: PADDOCK (NCT02588833), a phase Ib, multiple-ascending dose pilot trial with two cohorts, and PALOMINO (NCT03593200), a phase IIa, multiple-dose, single cohort trial using the same protocol and dosing schedule as Cohort 2 of the PADDOCK trial.<sup>68–70</sup> Both trials enrolled patients with PNH aged  $\geq 18$  years, PNH white blood cell clone size  $> 10\%$ , platelet count  $> 30,000/\text{mm}^3$ , absolute neutrophil count  $> 500/\text{mm}^3$ , LDH level  $\geq 2$  times the upper limit of normal (ULN) at the screening visit, and a history of receiving at least one blood transfusion within 12 months prior to screening.<sup>68,69</sup> Patients who had received prior eculizumab treatment were excluded from both trials. Pegcetacoplan (180–360 mg/day dosing range) was administered subcutaneously or via subcutaneous infusion when the dosing volume was  $> 3$  ml. The PADDOCK trial enrolled 3 patients in Cohort 1 and 20 patients in Cohort 2; 1 patient entered both cohorts.<sup>68</sup> The PALOMINO trial enrolled 4 patients.<sup>68</sup>

The PADDOCK and PALOMINO trials' primary efficacy endpoints were change from baseline in LDH, haptoglobin, and hemoglobin levels. In both trials,<sup>68</sup> improvements were observed at Day 365 after initiation of pegcetacoplan dosing in LDH (from  $> 8$  times the ULN to  $< 2$  times the ULN), hemoglobin (from below the LLN to within normal range), and haptoglobin levels (Table 1). Improvements were also observed for ARC, total bilirubin levels, and mean FACIT-Fatigue scores (i.e. a clinically meaningful improvement of  $\geq 3$ -points)<sup>35</sup> in both trials (Table 1).<sup>68</sup> After initiation of pegcetacoplan, 65% of PADDOCK patients and 100% of PALOMINO patients were transfusion-free (Table 1).<sup>68</sup> Categorized hematologic response to treatment

**Table 1.** Key endpoints from the pegcetacoplan phase I (PADDOCK)<sup>68</sup>, phase II (PALOMINO)<sup>68</sup> and phase III (PEGASUS<sup>66,71,72</sup> and PRINCE<sup>73</sup>) clinical trials.

	PADDOCK <sup>a</sup> (Day 365) <sup>68</sup>		PALOMINO <sup>a</sup> (Day 365) <sup>68</sup>		PEGASUS <sup>a</sup> (Week 16) <sup>66,71</sup>		PEGASUS <sup>a</sup> (Week 48) <sup>72</sup>		PRINCE <sup>a</sup> (Week 26) <sup>73</sup>		
	Pegcetacoplan	Pegcetacoplan	Pegcetacoplan	Pegcetacoplan	Pegcetacoplan	Eculizumab	Pegcetacoplan	Eculizumab	Pegcetacoplan	Eculizumab	Control treatment <sup>b</sup>
Hemoglobin, mean (SD), g/dL (NRR: females 12–16; males 13.6–18)	12.1 (2.0)	13.0 (2.2)	13.0 (2.2)	11.5 (2.0)	8.6 (1.0)	11.3 (1.8)	11.6 (2.2)	12.8 (2.1)	9.8 (2.4)		
LDH, mean (SD), U/L (PADDOCK/PALOMINO NRR: 120–250; PEGASUS NRR: 113–226)	306.5 (324.7)	226.0 (27.0)	189.0 (78.1)	353.0 (477.5)	224.1 (133.5)	204.6 (90.0)	1535.0 (751.6)				
ARC, mean (SD), × 10 <sup>9</sup> /L (PADDOCK/PALOMINO NRR: 10–110; PEGASUS NRR: 30–120)	96.4 (33.4)	94.0 (26.9)	77.0 (26.6)	221.0 (88.7)	80.0 (26.8)	94.0 (50.1)					
Total bilirubin, mean (SD), mg/dL (PADDOCK/PALOMINO NRR: 3–20; PEGASUS NRR: 1.7–18.8)	13.9 (5.6)	9.3 (8.2)									
FACIT-Fatigue, mean (SD) (Population norm: 43.6) <sup>33</sup>	42.5 (8.5)	47.0 (2.5)	41.8 (9.6)	30.6 (11.8)	42.5 (8.7)	45.3 (7.3)	39.6 (10.3)				
Haptoglobin, mean (SD), g/L (NRR: 0.14–2.58)	0.1 (0.1)	0.18 (0.2)									
Freedom from transfusions <sup>c</sup> , n (%)	13 (65.0)	4 (100.0)	35 (85.4)	6 (15.4)	28 (78.0)	32 (91.4)	1 (5.6)				
Clonal distribution of type II and type III PNH RBCs, % mean (SD)	84.0 (21.0)	93.0 (6.3)	93.9 (6.4)	62.6 (26.0)							
C3 deposition on type II and type III PNH RBCs, % mean (SD)	0.4 (0.6)	0.1 (0.1)	0.2 (0.3)	16.9 (15.5)							

ARC, absolute reticulocyte count; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy Fatigue scale; LDH, lactate dehydrogenase; NRR, normal reference range; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; SD, standard deviation.

<sup>a</sup>Data included in this table represent any publicly available data for these trials at the time of submission of this review article.

<sup>b</sup>Supportive treatment, including blood transfusions, anticoagulants, corticosteroids, and supplements (iron, folate, and vitamin B12).

<sup>c</sup>Also known as transfusion avoidance.





To reduce the burden of daily dosing on patients and to promote compliance, a twice weekly dosing regimen of 1080 mg via subcutaneous infusion was selected for the phase III trial based on preliminary pharmacokinetic data and modeling.<sup>13,64</sup> Data from the PEGASUS trial demonstrated that patients with PNH reached steady-state serum concentrations of pegcetacoplan (655–706 µg/mL) approximately 4–6 weeks following the first dose.<sup>13,66</sup>

At Week 16, pegcetacoplan was superior to eculizumab for the primary endpoint of change in hemoglobin level from baseline, with an adjusted (least squares) mean difference of 3.84 g/dL ( $p < 0.0001$ ; Table 1).<sup>66</sup> Pegcetacoplan was also superior to eculizumab at Week 16 for the secondary endpoint of hemoglobin normalization (defined as hemoglobin level  $\geq$  the LLN range) in the absence of transfusions, while non-inferiority was shown for secondary endpoints of freedom from transfusions (also known as transfusion avoidance) and ARC, but not for LDH.<sup>66</sup> Clinically meaningful improvements of  $\geq 3$ -points<sup>35</sup> in FACIT-Fatigue score were seen in patients receiving pegcetacoplan, but not eculizumab (Table 1).<sup>66</sup> Additional subgroup analyses according to pre-trial transfusion requirements revealed that improvements in hemoglobin levels from baseline were similar among pegcetacoplan-treated patients who received  $< 4$  or  $\geq 4$  transfusions in the 12 months before screening ( $< 4$ : 2.97 g/dL and  $\geq 4$ : 2.11 g/dL).<sup>66</sup> In contrast, eculizumab-treated patients who received  $< 4$  transfusions in the 12 months before screening only had a hemoglobin level decrease of 0.001 g/dL compared to 4.02 g/dL in the  $\geq 4$  transfusions group.<sup>66</sup> These data demonstrate that even patients who have a high transfusion requirement before the trial can benefit from pegcetacoplan treatment. In addition, although 27% of the patients randomized to the pegcetacoplan arm had a history of bone marrow failure with aplastic anemia, the inclusion of these patients in the study had no apparent negative effects on the efficacy results for pegcetacoplan.

Categorization of hematologic response to treatment, per criteria defined by Risitano *et al.* in 2019,<sup>59</sup> revealed that 7% of patients in the pegcetacoplan arm and 3% of patients in the eculizumab arm exhibited a good, major, or complete hematologic response at baseline.<sup>71</sup> At Week 16, 73% of patients receiving pegcetacoplan and 5%

of patients receiving eculizumab exhibited this response ( $p < 0.0001$ ).<sup>71</sup> Patients in the pegcetacoplan arm showed an improved mean score on all EORTC QLQ-C30 functional scales and the global health status/QoL measure at Week 16, while patients in the eculizumab arm showed a mean decrease from baseline.<sup>76</sup> Significant improvements in fatigue and dyspnea symptoms were also observed for pegcetacoplan-treated versus eculizumab-treated patients as measured by the EORTC QLQ-C30.<sup>76</sup>

The safety profile of pegcetacoplan was comparable to that of eculizumab.<sup>66</sup> The most common TEAEs for patients receiving pegcetacoplan were injection site reactions (36.6%) and diarrhea (22.0%; Table 2).<sup>66</sup> No cases of meningitis or thrombosis were reported (Table 2).<sup>66</sup> Three patients in the pegcetacoplan arm discontinued the trial before Week 16 due to investigator-reported breakthrough hemolysis.<sup>66</sup>

Overall, pegcetacoplan demonstrated superiority to eculizumab for the primary endpoint during the 16-week randomized controlled period and was associated with improved clinical outcomes in patients with PNH.

*Forty-eight-week endpoint: 32-Week open-label period.* All 77 patients who completed the PEGASUS 16-week randomized controlled period entered the 32-week open-label period as part of a pegcetacoplan-to-pegcetacoplan ( $n = 38$ ) or eculizumab-to-pegcetacoplan ( $n = 39$ ) arm.<sup>72</sup> Pegcetacoplan-to-pegcetacoplan patients completed 32 weeks of pegcetacoplan monotherapy, while eculizumab-to-pegcetacoplan patients completed a 4-week run-in period of dual therapy with eculizumab with pegcetacoplan before switching to pegcetacoplan monotherapy for 28 weeks.<sup>72</sup>

Pegcetacoplan-to-pegcetacoplan patients maintained comparably high mean hemoglobin levels between Week 16 and Week 48 ( $p = 0.140$ ), while eculizumab-to-pegcetacoplan patients demonstrated significantly higher mean hemoglobin levels at Week 48 as compared with Week 16 ( $p < 0.0001$ ; Table 1).<sup>72</sup> Over 70% of all patients in the trial were transfusion-free at Week 48 (Table 1). Improvements in ARC, LDH level, and FACIT-Fatigue score (i.e. a clinically meaningful improvement of  $\geq 3$ -points)<sup>35</sup> were maintained in the pegcetacoplan-to-pegcetacoplan arm and

observed in the eculizumab-to-pegcetacoplan arm from Week 16 to Week 48 (Table 1).<sup>72</sup> Categorization of hematologic response to treatment at Week 48, per criteria defined by Risitano *et al.*,<sup>59</sup> revealed that 63% of patients in the pegcetacoplan-to-pegcetacoplan arm ( $p=0.4142$  versus 73% at Week 16) and 54% of patients in the eculizumab-to-pegcetacoplan arm ( $p<0.0001$  versus 5% at Week 16) achieved a good, major, or complete hematologic response.<sup>77</sup> At Week 48, patients in both arms showed improvements in QoL, as evidenced by an increased score from baseline on all EORTC QLQ-C30 functional scales and the global health status/QoL measure.<sup>78</sup> Improvements in fatigue and dyspnea were also observed in both groups at Week 48 as indicated by EORTC QLQ-C30 symptom scores and were closer to the population norms.<sup>78</sup>

There was no significant change in safety profile with pegcetacoplan dosing up to 48 weeks of treatment.<sup>72</sup> The most common TEAEs for all patients who received pegcetacoplan were injection site reactions (26.0%) and hemolysis (19.5%).<sup>72</sup> Injection site reactions decreased in frequency as the trial progressed, suggesting that these events may be less likely as patients gain experience with subcutaneous self-administration of pegcetacoplan.<sup>79</sup> No cases of meningitis were reported throughout the trial (Table 2).<sup>72</sup> Thirteen patients, however, discontinued the trial prior to Week 48 due to a TEAE, including six discontinuations due to investigator-reported breakthrough hemolysis.<sup>72</sup>

Overall, results of the PEGASUS trial demonstrated that in patients with PNH and suboptimal response to prior eculizumab treatment, pegcetacoplan treatment for up to 48 weeks is durably effective and well-tolerated.

#### PRINCE

PRINCE (NCT04085601) was a phase III, multicenter, randomized, open-label, controlled trial evaluating the efficacy and safety of pegcetacoplan compared with control treatment (supportive care, including blood transfusions, anti-coagulants, corticosteroids, and supplements [iron, folate, and vitamin B12]) in complement-inhibitor-naïve patients with PNH.<sup>73,80</sup> A total of 53 patients aged  $\geq 18$  years with hemoglobin levels below the LLN (males:  $\leq 13.6$  g/dl; females:  $\leq 12.0$  g/dl), LDH levels  $\geq 1.5$  times the

ULN ( $1.5 \times$  ULN;  $\geq 339$  U/L), and a history of being complement-inhibitor-naïve (i.e. no treatment with eculizumab or ravulizumab within the 3 months before screening) were enrolled in the trial.<sup>80</sup> Patients were randomized 2:1 to receive pegcetacoplan (1080 mg subcutaneously twice weekly [ $n=35$ ]) or control treatment ( $n=18$ ) through Week 26.<sup>73</sup>

Pegcetacoplan was superior to control treatment in both co-primary endpoints of hemoglobin stabilization (i.e. avoidance of a  $>1$  g/dL decrease in hemoglobin level in the absence of blood transfusions) and change in LDH level from baseline to Week 26.<sup>73</sup> Hemoglobin stabilization was achieved by 85.7% ( $n=30$ ) of patients treated with pegcetacoplan and 0.0% of control arm patients through Week 26 ( $p<0.0001$ ). Pegcetacoplan-treated patients demonstrated superior reductions in mean LDH levels from baseline to Week 26 compared to control arm patients (least-squares mean change from baseline: pegcetacoplan,  $-1870.5$  U/L; control,  $-400.1$  U/L;  $p<0.0001$ ). Pegcetacoplan was also superior to control treatment for secondary endpoints, change from baseline in hemoglobin levels and transfusion avoidance. Larger mean hemoglobin level increases were observed in the pegcetacoplan group versus the control group, and 91.4% of pegcetacoplan-treated patients versus 5.6% of patients who received control treatment achieved transfusion avoidance.<sup>73</sup>

Serious AEs were reported by 8.7% ( $n=4$ ) of pegcetacoplan-treated patients and 16.7% ( $n=3$ ) of control arm patients through Week 26 (Table 2).<sup>73</sup> Two deaths deemed unrelated to treatment occurred (pegcetacoplan, 2.9%,  $n=1$ , septic shock related to medullary aplasia; control, 5.6%,  $n=1$ , respiratory failure).<sup>73</sup> The most common TEAEs reported during the trial were injection site reactions (pegcetacoplan, 30.4%,  $n=14$ ; control, 0.0%; Table 2), hypokalemia (pegcetacoplan, 13.0%,  $n=6$ ; control, 11.1%,  $n=2$ ), and fever (pegcetacoplan, 8.7%,  $n=4$ ; control, 0.0%).<sup>73</sup> No cases of meningitis or thrombosis were reported in either group (Table 2) and no TEAEs led to discontinuation of pegcetacoplan.<sup>73</sup>

Patients with PNH who were naïve to complement-inhibitor treatment demonstrated meaningful hematological and clinical improvements following 26 weeks of pegcetacoplan treatment in PRINCE. The pegcetacoplan safety profile was similar to previous trials. These results provide

evidence for the safety and efficacy of pegcetacoplan treatment in complement-inhibitor-naïve patients with PNH.

### Conclusion and future directions

Results from phase I–III clinical trials suggest that pegcetacoplan is efficacious and safe in a broad population of patients with PNH. This has been demonstrated among patients with suboptimal response to prior C5i therapy who achieved superior hemoglobin level improvements with pegcetacoplan compared to eculizumab. In addition, superior hematologic improvements were also achieved with pegcetacoplan versus standard treatment (excluding complement-inhibitors) in complement-inhibitor-naïve patients.

Pegcetacoplan presented a favorable safety profile with injection site reactions being the most common TEAE. As expected, rates of injection site reactions decreased as the trials progressed. This finding was consistent with the assumption that these events would become less common as patients gained experience with pegcetacoplan self-administration and were not a barrier to treatment,<sup>79</sup> as numerous QoL gains were reported by patients. No meningococcal infections, a potential concern with complement inhibition, have been observed during clinical studies with pegcetacoplan, indicating that mitigation plans to prevent these infections (i.e. vaccination strategy and prophylactic antibiotic treatment) are effective.<sup>66,72,73</sup>

Pegcetacoplan therapy for patients with PNH has been shown to have several benefits compared to treatment with other US FDA-approved therapies. In contrast to the requirement for intravenous dosing of eculizumab and ravulizumab, pegcetacoplan can be self-administered at home by the patient or a caregiver at their convenience (under guidance/training from a healthcare professional); thus eliminating the continuous need for an appointed nurse trained in intravenous drug administration and regular infusion clinic visits.<sup>8,9,81</sup> In addition to improved hematologic parameters, patients receiving pegcetacoplan have reported increased QoL measures (such as decreased fatigue levels) in various clinical trials of the drug.<sup>66,76,78</sup> A recent cost analysis demonstrated \$1.7 million in cost savings for one US health insurance payer over a 3-year period due to reduced transfusion requirements and fewer breakthrough hemolysis events when patients were treated with pegcetacoplan.<sup>82</sup>

In May 2021, pegcetacoplan (Empaveli) became the first C3-targeted PNH therapy to be approved by the US FDA for the treatment of adults with PNH, including those who have switched from treatment with C5i therapies eculizumab and ravulizumab.<sup>13</sup> Shortly after, pegcetacoplan was approved for adults with PNH who remain anemic despite stable C5i therapy for at least 3 months by the EMA in December 2021 (Aspaveli),<sup>14</sup> and by the Australian Therapeutic Goods Agency in February 2022 (Empaveli; also approved for patients intolerant to C5i therapy).<sup>15</sup> Pegcetacoplan's official label dosing regimen is 1080 mg/20 ml injection volume twice weekly, administered as a subcutaneous infusion through an infusion pump (with a reservoir of at least 20 ml).<sup>13</sup> For patients switching from C5i therapy, pegcetacoplan should be administered concomitantly with the preexisting therapy for 4 weeks, after which the C5i is discontinued.<sup>13</sup> Due to complement-inhibitor usage carrying a risk of infection by encapsulated bacteria, the United States prescribing information carries a boxed warning for infections with *Neisseria meningitidis* types A, C, W, Y and B, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B.<sup>13</sup> Recommended mitigation plans to prevent infections with encapsulated bacteria include vaccinations against *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type B at least 2 weeks prior to receiving pegcetacoplan, and antibacterial drug prophylaxis if an unvaccinated patient must receive pegcetacoplan immediately.<sup>13</sup>

Future investigations with pegcetacoplan for the treatment of PNH should be conducted to further clarify the risk of breakthrough hemolysis with pegcetacoplan, the drug's immunogenicity, and the long-term risk of encapsulated bacterial infection. Although incidences of breakthrough hemolysis were reported by investigators during the PEGASUS trial,<sup>66,72</sup> data for breakthrough hemolysis are not available using previously defined criteria (at least one new or worsening symptom/sign of intravascular hemolysis in the presence of elevated LDH levels after prior LDH level reduction while on therapy).<sup>8,9</sup> In addition, treatment with therapeutic peptides is associated with a concern for drug immunogenicity, and although the immunogenicity of pegcetacoplan has been evaluated and no apparent negative effects on the safety and efficacy of pegcetacoplan have been observed, the available methodology and data regarding the formation of antidrug antibodies have not been

adequate to fully evaluate the immunogenicity of pegcetacoplan.<sup>13</sup> Furthermore, real-world surveillance of encapsulated bacterial infections with pegcetacoplan is needed to fully understand the long-term risk of these infections with the drug and C3 inhibition. Of note, an extension study (NCT03531255) to investigate the long-term efficacy and safety of pegcetacoplan<sup>83</sup> and a phase II study (NCT04901936) investigating the efficacy and safety of pegcetacoplan in children with PNH are currently ongoing.<sup>84</sup>

Pegcetacoplan is also being investigated for the treatment of other complement-mediated conditions, including age-related macular degeneration (AMD), geographic atrophy (GA), C3 glomerulopathy, and cold agglutinin disease. Treatment with pegcetacoplan has been shown to significantly reduce the growth rate of GA lesions in adults with GA secondary to AMD in the phase II FILLY trial (NCT02503332)<sup>85</sup> and the phase III OAKS trial (NCT03525613).<sup>86,87</sup> In addition, although pegcetacoplan-treated patients with GA secondary to AMD in the phase III DERBY trial (NCT03525600) narrowly missed the primary endpoint of reduction in GA lesions at Month 12 of the study,<sup>86</sup> longer-term analysis of patients has demonstrated that pegcetacoplan contributed to nominally significant reductions in GA lesion growth at Month 18.<sup>87</sup> Pegcetacoplan was also associated with a 73.3% reduction in proteinuria in five patients with C3 glomerulopathy in the phase II DISCOVERY trial (NCT03453619)<sup>88</sup> and demonstrated preliminary efficacy in patients with cold agglutinin disease in the PLAUDIT trial (NCT03226678).<sup>89</sup> It is likely that pegcetacoplan's approved usage will be expanded to some of these conditions in the future, although the dosage and route of administration remains to be determined.

Increasing interest in the field of complement therapeutics has prompted the execution of numerous preclinical and clinical trials using novel complement-inhibitors and agents.<sup>59</sup> As new complement-targeting therapies are approved, the efficacy of these novel therapeutics as both primary and combinational therapy options should be investigated. Most of the novel therapies in development are proximal complement-inhibitors representing three strategic target categories: anti-C3 agents, anti-factor D agents, and anti-factor B agents.<sup>59</sup> Factor D and factor B are complement

mediators within the alternative complement pathway, one of the three pathways capable of initiating the processes that result in C3 activation.<sup>90</sup> Proximal complement-inhibitors within these categories are currently under investigation for oral or subcutaneous administration for patients with PNH as monotherapy or in association with C5i therapy.<sup>59</sup> Ultimately, pegcetacoplan has demonstrated clinically compelling evidence for the efficacy and safety of proximal complement inhibition in patients with PNH. Thus, pegcetacoplan together with the development of other novel therapeutics provide hope for the future of effective treatment options for the optimal management of PNH and other complement-mediated diseases.

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Author contribution(s)*

**Raymond S.M. Wong:** Conceptualization; Writing – original draft; Writing – review & editing.

### *Acknowledgements*

The author thanks Francie Moehring, PhD, Nicole Green, MD, and Apeksha Shenoy, MSE of Boston Strategic Partners, Boston, MA, USA for their medical writing support, editorial support, and assistance with article submission on the author's behalf (funded by Apellis Pharmaceuticals, Inc). The author approves of the article's content, accuracy, and integrity per ICMJE criteria, and all statements and declarations contained therein. Apellis Pharmaceuticals, Inc and Swedish Orphan Biovitrum AB reviewed the article.

### *Funding*

The author disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Apellis Pharmaceuticals, Inc.

### *Competing interests*

The author declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

Raymond S.M. Wong: Alexion Consultancy, Honoraria, Research Funding and Speakers Bureau, Apellis Research Funding and Speakers Bureau, Roche Consultancy, Honoraria, Research Funding and Speakers Bureau

#### Availability of data and materials

Not applicable.

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