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ORIGINAL RESEARCH

Safety and Efficacy of Pegcetacoplan in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria over 48 Weeks: 307 Open-Label Extension Study

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ABSTRACT

Introduction: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening disease characterized by complement-mediated hemolysis and thrombosis. Pegcetacoplan, the first targeted complement component 3 (C3) PNH therapy, was safe and efficacious in treatment-naive and pre-treated patients with PNH in five clinical trials.

Methods: The 307 open-label extension (OLE) study (NCT03531255) is a non-randomized, multicenter extension study of long-term safety and efficacy of pegcetacoplan in adult patients with PNH who completed a pegcetacoplan parent study. All patients received pegcetacoplan. Outcomes at the 48-week data cutoff (week 48 of 307-OLE or August 27, 2021, whichever was earlier) are reported. Hemoglobin concentrations, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores, and transfusion avoidance were measured. Hemoglobin > 12 g/dL and sex-specific hemoglobin normalization (i.e., male, ≥ 13.6 g/dL; female, ≥ 12 g/dL) were assessed as percentage of patients with data available and no transfu-

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sions 60 days before data cutoff. Treatment-emergent adverse events, including hemolysis, were reported.
Results: Data from 137 patients with at least one pegcetacoplan dose at data cutoff were analyzed. Mean (standard deviation [SD]) hemoglobin increased from 8.9 (1.22) g/dL at parent study baseline to 11.6 (2.17) g/dL at 307-OLE entry and 11.6 (1.94) g/dL at data cutoff. At parent study baseline, mean (SD) FACIT-Fatigue score of 34.1 (11.08) was below the general population norm of 43.6; scores improved to 42.8 (8.79) at 307-OLE entry and 42.4 (9.84) at data cutoff. In evaluable patients, hemoglobin > 12 g/dL occurred in 40.2% (43 of 107) and sex-specific hemoglobin normalization occurred in 31.8% (34 of 107) at data cutoff. Transfusion was not required for 114 of 137 patients (83.2%). Hemolysis was reported in 23 patients (16.8%). No thrombotic events or meningococcal infections occurred.
Conclusion: Pegcetacoplan sustained long-term improvements in hemoglobin concentrations, fatigue reduction, and transfusion burden. Long-term safety findings corroborate the favorable profile established for pegcetacoplan.
Trial Registration: ClinicalTrials.gov identifier, NCT03531255.

Keywords: Complement inhibitor; Clinical trial; Eculizumab; FACIT-Fatigue; Hemoglobin; Open-label extension; Pegcetacoplan; Paroxysmal nocturnal hemoglobinuria (PNH); Thrombosis; Transfusion

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Key Summary Points

Why carry out this study?

Paroxysmal nocturnal hemoglobinuria (PNH), a rare, complement-mediated blood disorder characterized by life-threatening hemolysis and thrombosis, is typically treated with complement component 5 (C5) inhibitors, which control intravascular hemolysis to improve clinical outcomes and decrease mortality; however, outcomes with C5 inhibitors can be suboptimal.

This study was carried out to collect long-term data about the safety and efficacy of pegcetacoplan, a targeted complement component 3 (C3) therapy for PNH, which can control both intravascular and extravascular hemolysis.

What did the study ask?

This 307 open-label extension (OLE) study assessed the long-term safety and efficacy of pegcetacoplan in patients with PNH from five clinical trials (PHAROAH and PADDOCK [phase 1], PALOMINO [phase 2], and PEGASUS and PRINCE [phase 3]).

What were the study outcomes?

Pegcetacoplan provided sustained, robust efficacy in patients with PNH at this 48-week data cutoff of the 307-OLE, with some patients having normalized hemoglobin concentrations, normalized lactate dehydrogenase concentrations, and normalized Functional Assessment of Chronic Illness Therapy-Fatigue scores, and the majority of patients not requiring a transfusion; the adverse event profile for pegcetacoplan was consistent with that established in pivotal trials and there were no reports of thrombotic events or meningococcal infections in the 307-OLE at the data cutoff.

What has been learned from the study?

These results support consistent safety and continued efficacy of pegcetacoplan, a novel PNH treatment option that inhibits earlier steps of complement pathway activation by targeting C3.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening disease characterized by complement-mediated hemolysis and thrombosis [1]. Patients with PNH have an acquired mutation in *PIG-A*, leading to the lack of glycosylphosphatidylinositol (GPI) anchors in hematopoietic stem cells required for cell surface expression of regulatory proteins [2]. While bone marrow dysfunction is common in PNH, the absence of regulatory proteins like CD55 and CD59 results in premature destruction of red blood cells via complement-mediated hemolysis, potentially leading to an increased risk of thrombosis [3, 4].

The first targeted treatments for PNH, eculizumab and ravulizumab, inhibit complement component 5 (C5), blocking formation of the membrane attack complex (MAC) and intravascular hemolysis (IVH) [5–10]. In phase 3 studies, C5 inhibitors improved outcomes in patients with PNH, demonstrating lower lactate dehydrogenase (LDH) concentrations, stabilized hemoglobin concentrations, fewer transfusions, and reduced fatigue compared with baseline [6–10]. Eculizumab improves survival in patients with PNH versus supportive care alone [11]. Despite improvements with C5 inhibitors, a considerable proportion of patients have ongoing disease burden, including continued transfusion needs, suboptimal hemoglobin concentrations, and fatigue [6–10, 12–15]. These residual sequalae are potentially due to extravascular hemolysis (EVH) mediated by complement component 3 (C3), which targets red blood cells for upstream removal in the liver and spleen through opsonization [3, 16, 17].

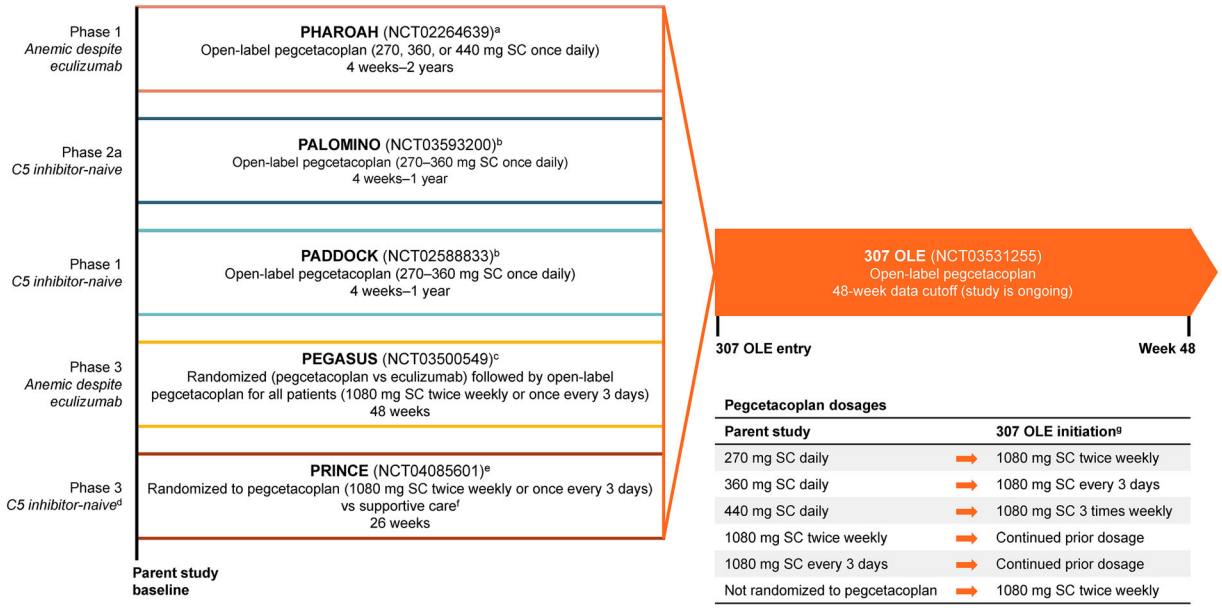


Fig. 1 Summary of the parent study background and the subsequent 307-OLE of pegcetacoplan in patients with PNH. *C5* complement component 5, *OLE* open-label extension, *PNH* paroxysmal nocturnal hemoglobinuria, *SC* subcutaneous. [a]Source: de Castro and colleagues [27]. [b]Source: Wong and colleagues [28]. [c]Sources: Hillmen and colleagues [24], de Latour and colleagues [25]. [d]Patients had not received complement inhibitor treatment within 3 months prior to screening. [e]Source: Wong and colleagues [26]. [f]Supportive care included blood transfusions, anticoagulants, corticosteroids, and supplements (iron, folate, and vitamin B_{12}). [g]Dosage increases were considered for patients with LDH > 2 × the upper limit of normal on one occasion while receiving pegcetacoplan. Eculizumab and ravulizumab were permitted as rescue treatments for acute breakthrough hemolysis

Pegcetacoplan is the first targeted C3 therapy approved for the treatment of patients with PNH by the US Food and Drug Administration. Pegcetacoplan is also approved for adults with PNH plus anemia despite receiving a C5 inhibitor for at least 3 months by the European Medicines Agency and the National Institute for Health and Care Excellence, and by other agencies (e.g., the Canadian Agency for Drugs and Technologies in Health) [18–23]. Two phase 3 studies, PEGASUS and PRINCE, demonstrated pegcetacoplan efficacy and safety in patients with PNH [24–26]. In PEGASUS, pegcetacoplan-treated patients with PNH who had anemia despite eculizumab treatment had increased hemoglobin concentrations, reduced transfusion burdens, decreased absolute reticulocyte counts, and less fatigue [24, 25]. In addition, hemoglobin and LDH normalization were observed in greater percentages of patients who received pegcetacoplan versus eculizumab [24]. In the PRINCE trial of patients with PNH who were naive to complement inhibitors, pegcetacoplan increased hemoglobin concentrations and reduced LDH concentrations, and the improvements were maintained for 26 weeks [26]. With pegcetacoplan, 91% of patients had not required a transfusion through week 26 [26]. Nearly half of pegcetacoplan-treated patients in PRINCE had hemoglobin normalization at study end, 60% had absolute reticulocyte count normalization, and nearly two-thirds had LDH normalization [26].

The 307 open-label extension (307-OLE) study is a multicenter, non-randomized extension of the five completed clinical trials of pegcetacoplan in patients with PNH (PHAROAH and PADDOCK [phase 1], PALOMINO [phase 2], and PEGASUS and PRINCE [phase 3]). Here we report the long-term safety and efficacy of

pegcetacoplan at data cutoff, defined as either week 48 of the 307-OLE or August 27, 2021, whichever was earlier.

METHODS

Patients and Study Design

The 307-OLE (NCT03531255) is a multicenter extension study of long-term safety and efficacy of pegcetacoplan in adult patients with PNH who participated in a previous pegcetacoplan phase 1 (PHAROAH, PADDOCK), phase 2 (PALOMINO), or phase 3 (PEGASUS, PRINCE) parent study [24–28]. Study design details of all parent studies have been published [24–28] and are summarized in Fig. 1.

Patients with PNH were eligible for the 307-OLE if they had participated in a parent trial and both the patient and physician wanted to continue or initiate pegcetacoplan treatment because of potential clinical benefit and acceptable tolerability. Patients who had withdrawn from or discontinued a pegcetacoplan trial were excluded. Patients receiving concomitant complement inhibitor treatment, with concurrent severe aplastic anemia, or with a history of hereditary complement deficiency, bone marrow transplant, or meningococcal disease were also excluded.

All patients in the 307-OLE received pegcetacoplan subcutaneously. As shown in Fig. 1, starting pegcetacoplan dosages in the 307-OLE were 1080 mg twice weekly, every 3 days, or three times weekly, depending on the dosage received in the parent study. A dosage increase to 1080 mg every third day was considered for patients with LDH $> 2 \times$ the upper limit of normal (ULN) on one occasion while receiving pegcetacoplan to control acute hemolysis; a dosage increase to 1080 mg three times weekly was considered for patients with LDH $> 2 \times$ ULN on one occasion while receiving pegcetacoplan 1080 mg every third day. Eculizumab and ravulizumab were permitted as rescue treatments for acute breakthrough hemolysis.

Outcomes

This report presents data available at data cutoff, defined as week 48 of 307-OLE or August 27, 2021, whichever was earlier. The study is ongoing. Pegcetacoplan exposure was summarized as the number and percentage of patients who received a maximum dosage of pegcetacoplan 1080 mg twice weekly, once every 3 days, or three times per week during the OLE. The treatment duration and percentage of patients who had received 48 weeks of pegcetacoplan in the 307-OLE at data cutoff were determined. Treatment compliance was defined as the total number of study injections from day 1 of the 307-OLE to data cutoff divided by the total number of expected injections during that time, adjusted to reflect the actual planned dosing frequency. Demographics and clinical characteristics were recorded at 307-OLE entry.

Hemoglobin and LDH concentrations and FACIT-Fatigue scores were measured at 307-OLE entry and weeks 4, 12, 24, 36, and 48. Scores for FACIT-Fatigue range from 0 to 52, with higher scores indicating less fatigue; a score of 43.6 is the general population norm [29]. Red blood cell transfusion avoidance (i.e., not requiring a transfusion from the beginning of the 307-OLE through data cutoff) was measured at the 48-week data cutoff. Transfusion needs were determined by the investigator on the basis of standard of care and according to local clinical practice and individual patient management. Patients who withdrew did not meet the transfusion avoidance criterion.

Incidence of any adverse events (AEs) and treatment-emergent AEs (TEAEs) was coded to System Organ Class and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 23.0. A TEAE was defined as an AE that occurred or worsened after the first dose of pegcetacoplan in the 307-OLE for up to 30 days after the last pegcetacoplan dose. Investigators assessed each AE as related or not related to pegcetacoplan. A serious AE was any AE that either the investigator or sponsor deemed as having resulted in death, was life-

threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or was a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization were considered serious when they jeopardized the patient or required medical or surgical intervention to prevent outcomes that characterize serious AEs.

Events of hemolysis were identified by TEAEs coded with the PT of hemolysis. Event intensity was determined by the investigating physicians. Records for patients with TEAEs of hemolysis events were reviewed to determine the numbers of patients with complement-amplifying conditions (CACs), transfusions related to hemolysis events, pegcetacoplan dose adjustments, eculizumab or ravulizumab treatment, study discontinuation, and recovery. Events of infection, injury, vaccination, or pregnancy were considered CACs.

Additional Analyses

Hemoglobin, LDH, and FACIT-Fatigue score values at baseline of the parent study were assessed for the intention-to-treat (ITT) population of the 307-OLE in total and by parent study populations in PADDOCK, PALOMINO, PEGASUS, and PRINCE. Parent study baseline data for PHAROAH patients were not included. Hemoglobin > 12 g/dL and normalization of hemoglobin (i.e., at or above the sex-specific lower limit of normal [LLN; 13.6 g/dL for male patients, 12 g/dL for female patients]) and LDH (i.e., at or below ULN [226 U/L]) at 307-OLE data cutoff were assessed as percentages of patients in total and each parent study population with data available and no transfusions 60 days prior to data cutoff. Normal ranges were defined by the central laboratory. Local laboratory values were normalized to the normal range of the central laboratory. The percentage of patients with D-dimer normalization, defined as at or below ULN (0.5 mg/L fibrinogen equivalent units), was assessed in the total 307-OLE population at 307-OLE entry and weeks 4, 12, 24, 36, and 48.

Statistical Analysis

Exposure, efficacy, and safety analyses were performed in the ITT population, which included all patients who enrolled and received at least one dose of pegcetacoplan in the 307-OLE. Patient characteristics, efficacy, and safety were presented by parent study and total 307-OLE population. Continuous data were summarized using descriptive statistics (number of patients, mean, median, standard deviation [SD], interquartile range [IQR], range), and categorical data were summarized as the number and percentage of patients. Missing data were not imputed. Patients who withdrew from the study, were missing data at the specified timepoint, or received transfusions during the 60 days prior to data cutoff were classified as non-responders for normalization.

Study Approval

Parent study and 307-OLE protocols were designed and monitored in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki [24–28]. These protocols were approved by an institutional review board or independent ethics committee at each center. Each patient provided written informed consent before undergoing study-related procedures.

RESULTS

Patient Disposition

In all, 137 of 145 patients with PNH (94.5%) who completed a pegcetacoplan trial entered the 307-OLE. Four of four patients (100%) who completed the PHAROAH parent study [27], four of four (100%) who completed PALOMINO [28], 15 of 20 (75.0%) who completed PADDOCK [28], 64 of 67 (95.5%) who completed PEGASUS [25], and 50 of 50 (100%) who completed PRINCE [26] entered the 307-OLE. All

Table 1 Patient disposition through the 48-week data cutoff in the 307-OLE for patients with PNH

n (%)	Parent study					Total *N* = 137
	PHAROAH *N* = 4	PALOMINO *N* = 4	PADDOCK *N* = 15	PEGASUS *N* = 64	PRINCE *N* = 50	
Received ≥ 1 pegcetacoplan dose	4 (100)	4 (100)	15 (100)	64 (100)	50 (100)	137 (100)
Withdrawn from study	0	0	1 (6.7)	6 (9.4)	1 (2.0)	8 (5.8)
Primary reasons for study withdrawal						
Adverse event	0	0	0	3 (4.7)	0	3 (2.2)
Lost to follow-up	0	0	0	1 (1.6)	0	1 (0.7)
Physician decision	0	0	0	2 (3.1)	0	2 (1.5)
Sponsor request[a]	0	0	1 (6.7)	0	0	1 (0.7)
Death	0	0	0	0	1 (2.0)	1 (0.7)

OLE open-label extension, *PNH* paroxysmal nocturnal hemoglobinuria
[a]In a joint decision made by the sponsor and the investigator

137 patients had received at least one dose of pegcetacoplan (ITT population) at data cutoff and were included in this analysis (Table 1). At data cutoff, eight patients had withdrawn from the 307-OLE (Table 1). The reasons for study withdrawal were adverse event (three patients from PEGASUS), physician decision (two patients from PEGASUS), loss to follow-up (one patient from PEGASUS), sponsor request (in a joint decision made with the investigator; one patient from PADDOCK), and death (one patient from PRINCE).

Pegcetacoplan Exposure

At 307-OLE entry, patients in the total population (*N* = 137) received pegcetacoplan 1080 mg twice weekly (122 patients, 89.1%), once every 3 days (14 patients, 10.2%), or three times per week (One patient, 0.7%). As of the data cutoff, the maximum dosing frequency was twice weekly for 104 patients (75.9%), once every 3 days for 25 (18.2%), and three times per week for eight (5.8%). Nearly all patients (134 patients, 97.8%) completed all injections. As of the data cutoff, 107 patients (78.1%) had completed 48 weeks of additional treatment with pegcetacoplan in the 307-OLE. The median (range) treatment duration was 48.1 (7.9–50.1) weeks.

Characteristics at 307-OLE Entry

Demographic and clinical characteristics and laboratory measurements at 307-OLE entry are shown in Table 2. In the total population, the mean (SD) patient age was 46.5 (14.6) years, and slightly more than half of the patients were female. The most common race was Asian (46.0%), followed by White (35.0%), Other (5.8%), American Indian or Alaska Native (3.6%), and Black or African American (2.2%). Most patients (81.0%) were not of Hispanic or Latino ethnicity.

Patients in the total population had a mean (SD) body mass index of 25.6 (5.3) kg/m^2 at 307-OLE entry. The median (IQR) time since PNH diagnosis was 6.9 (0.61–39.0) years. The median durations of PNH were shorter in studies of C5 inhibitor-naive patients (with the exception of PADDOCK) and longer in studies of patients with low hemoglobin despite eculizumab treatment.

At 307-OLE study entry, mean hemoglobin concentration was 11.6 g/dL for the total population, and hemoglobin concentrations were comparable across parent study populations.

Table 2 Demographic and clinical characteristics at 307-OLE entry for patients with PNH

	Parent study					Total *N* = 137
	PHAROAH *N* = 4	**PALOMINO** *N* = 4	**PADDOCK** *N* = 15	**PEGASUS** *N* = 64	**PRINCE** *N* = 50	
Demographics						
Age, years, mean (SD)	54.3 (3.6)	31.8 (11.8)	43.7 (14.4)	48.5 (15.2)	45.5 (14.0)	46.5 (14.6)
Female patients, *n* (%)	4 (100)	3 (75.0)	7 (46.7)	39 (60.9)	23 (46.0)	76 (55.5)
Race, *n* (%)						
American Indian or Alaska Native	0	0	0	0	5 (10.0)	5 (3.6)
Asian	0	0	14 (93.3)	11 (17.2)	38 (76.0)	63 (46.0)
Black or African American	1 (25.0)	0	0	2 (3.1)	0	3 (2.2)
White	3 (75.0)	4 (100)	1 (6.7)	40 (62.5)	0	48 (35.0)
Other	0	0	0	1 (1.6)	7 (14.0)	8 (5.8)
Not reported	0	0	0	10 (15.6)	0	10 (7.3)
Ethnicity, *n* (%)						
Hispanic or Latino	1 (25.0)	0	0	3 (4.7)	12 (24.0)	16 (11.7)
Not Hispanic or Latino	3 (75.0)	4 (100)	15 (100)	51 (79.7)	38 (76.0)	111 (81.0)
Not reported	0	0	0	10 (15.6)	0	10 (7.3)
Clinical characteristics						
BMI, kg/m^2, mean (SD)	*n* = 4	*n* = 4	*n* = 15	*n* = 54	*n* = 48	*n* = 125
	35.5 (14.0)	28.8 (4.7)	24.8 (4.7)	26.2 (4.5)	24.1 (4.3)	25.6 (5.3)
Time since PNH diagnosis, median (range), years	12.0 (11.0–24.0)	2.9 (1.9–8.0)	10.0 (3.3–35.0)	7.0 (2.0–39.0)	4.7 (0.6–28.0)	6.9 (0.6–39.0)
Laboratory measurements						
Hemoglobin, mean (SD), g/dL[a]	12.2 (0.4)	13.3 (2.3)	11.7 (2.2)	11.5 (1.8)	11.7 (2.6)	11.6 (2.2)
LDH, median (range), U/L[b]	*n* = 4	*n* = 4	*n* = 15	*n* = 63	*n* = 50	*n* = 136
	302.3	185.5	165.0	181.0	193.2	184.0
	(124–351)	(167–237)	(115–3459)	(69–801)	(109–2314)	(69–3459)
ARC, mean (SD),	*n* = 4	*n* = 4	*n* = 15	*n* = 60	*n* = 47	*n* = 130
× 10^9 cells/L[c]	88.8 (36.7)	72.5 (34.0)	90.0 (65.6)	80.3 (33.1)	99.6 (37.7)	88.4 (40.2)

Table 2 continued

	Parent study					Total $N = 137$
	PHAROAH $N = 4$	PALOMINO $N = 4$	PADDOCK $N = 15$	PEGASUS $N = 64$	PRINCE $N = 50$	
Indirect bilirubin, mean (SD), μmol/L[d]	$n = 4$	$n = 4$	$n = 15$	$n = 60$	$n = 50$	$n = 133$
	8.3 (1.4)	8.7 (6.0)	13.7 (8.9)	10.5 (6.1)	12.9 (8.6)	11.6 (7.5)
Patient-reported outcome						
FACIT-Fatigue score, mean (SD)[e]	$n = 4$	$n = 4$	$n = 15$	$n = 63$	$n = 49$	$n = 135$
	45.3 (4.1)	47.3 (1.5)	44.4 (6.2)	41.1 (10.0)	43.9 (8.2)	42.8 (8.8)

ARC absolute reticulocyte count, *BMI* body mass index, *FACIT-Fatigue* Functional Assessment of Chronic Illness Therapy-Fatigue, *LDH* lactate dehydrogenase, *OLE* open-label extension, *PNH* paroxysmal nocturnal hemoglobinuria, *SD* standard deviation

[a]Normal reference range male, 13.6–18 g/dL; female, 12–16 g/dL

[b]Normal reference range 113–226 U/L

[c]Normal reference range male, 10–140 × 10^9 cells/L; female, 10–120 × 10^9 cells/L

[d]Normal reference range 1.7–15.4 μmol/L

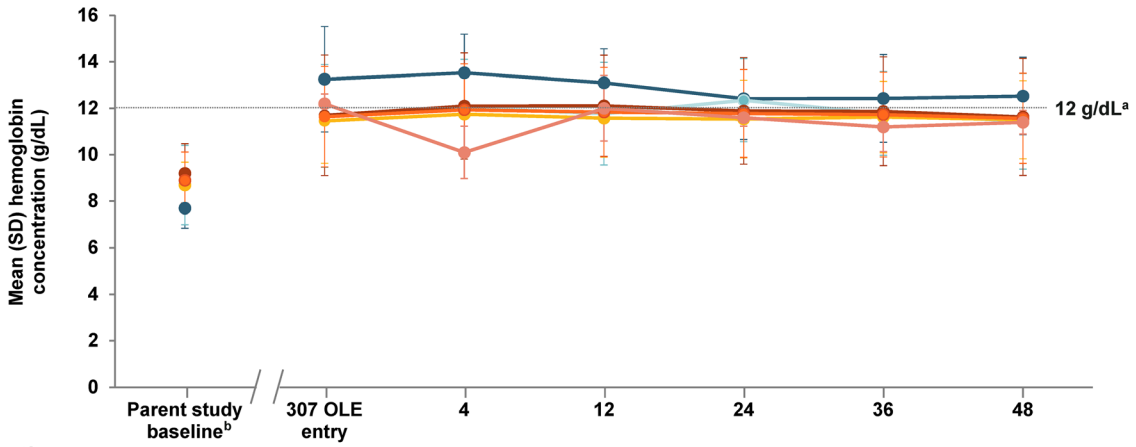
[e]General population norm 43.6. Defined by Cella et al. [29]

The median LDH concentration (184.0 U/L) was within the normal range (113–226 U/L) in the total population and in all parent study populations except PHAROAH, in which it was somewhat elevated (302.3 U/L). Across the parent study and total populations, the mean absolute reticulocyte counts were within normal limits (10–140 × 10^9 cells/L for male patients; 10–120 × 10^9 cells/L for female patients), as were indirect bilirubin concentrations (normal range 1.7–15.4 μmol/L). The mean FACIT-Fatigue scores were at or near the general population norm of 43.6 [29] in all populations.

Outcomes

Mean hemoglobin concentrations were below 12 g/dL (the LLN for female patients) at baseline of the parent studies in the total population and the four parent study populations analyzed (PALOMINO, PADDOCK, PEGASUS, PRINCE) (Fig. 2). Mean hemoglobin concentration for the total study population at baseline of the parent studies was 8.9 g/dL. By 307-OLE entry, hemoglobin concentrations approached 12 g/dL in the total population and all analyzed parent study populations except PALOMINO, which had a higher mean hemoglobin concentration of 13.3 g/dL. Concentrations remained stable through week 48 in all parent study populations, aside from week 4 in patients from PHAROAH, which only included two patients.

At parent study baseline, median LDH concentrations were markedly elevated in all analyzed parent study populations except PEGASUS, in which patients previously treated with eculizumab had concentrations near the ULN (Fig. 3). The median (IQR) LDH values at parent study baseline were as follows: 2585 (2098–3000) U/L (PALOMINO); 2734 (1579–3315) U/L (PADDOCK); 223 (194–271) U/L (PEGASUS); and 2038 (1410–2658) U/L (PRINCE). At 307-OLE entry, median LDH concentrations were within normal limits in the total population and all parent study populations except PHAROAH, which was $< 1.5 \times$ the ULN (i.e., 339 U/L). Median LDH concentrations were within the normal range from weeks 12 through 48 of the 307-OLE in all parent study populations.



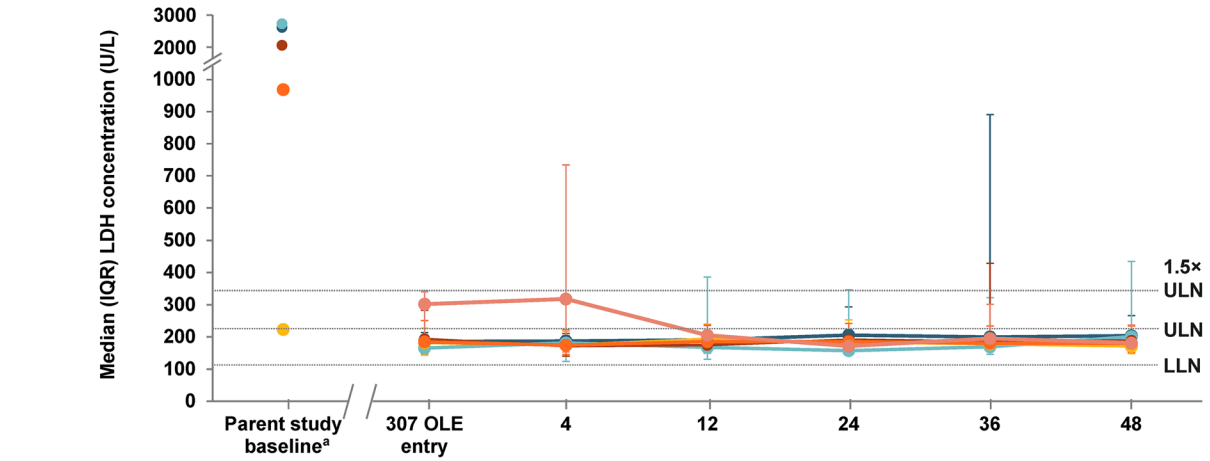
Mean (SD) hemoglobin (g/dL)							
PHAROAH (N=4)	NA	n=4 12.2 (0.42)	n=2 10.1 (1.13)	n=2 12.0 (1.41)	n=4 11.6 (0.37)	n=4 11.2 (1.07)	n=4 11.4 (0.51)
PALOMINO (N=4)	n=4 7.7 (0.86)	n=4 13.3 (2.27)	n=4 13.5 (1.66)	n=4 13.1 (1.47)	n=4 12.4 (1.76)	n=4 12.4 (1.89)	n=4 12.5 (1.67)
PADDOCK (N=15)	n=15 8.7 (1.71)	n=15 11.7 (2.22)	n=15 12.0 (2.08)	n=15 11.8 (2.21)	n=15 12.4 (1.79)	n=14 11.8 (1.80)	n=14 11.4 (2.06)
PEGASUS (N=64)	n=64 8.7 (0.98)	n=64 11.5 (1.83)	n=62 11.8 (1.66)	n=64 11.6 (1.68)	n=62 11.5 (1.68)	n=59 11.6 (1.54)	n=57 11.5 (1.68)
PRINCE (N=50)	n=50 9.2 (1.28)	n=50 11.7 (2.59)	n=49 12.1 (2.29)	n=45 12.1 (2.18)	n=41 11.9 (2.29)	n=34 11.9 (2.34)	n=28 11.6 (2.52)
Total (N=137)[c]	n=133[d] 8.9 (1.22)	n=137 11.6 (2.17)	n=132 11.9 (1.97)	n=130 11.8 (1.92)	n=126 11.8 (1.89)	n=115 11.7 (1.82)	n=107 11.6 (1.94)

Fig. 2 Concentrations of hemoglobin at baseline of the PALOMINO, PADDOCK, PEGASUS, and PRINCE parent studies and from 307-OLE entry to week 48 in the total and parent study populations of patients with PNH. *LLN* lower limit of normal, *NA* not available, *OLE* open-label extension, *PNH* paroxysmal nocturnal hemoglobinuria, *SD* standard deviation. [a]Hemoglobin LLN for female patients: 12 g/dL. [b]Patients in PALOMINO, PADDOCK, and PRINCE were complement inhibitor-naive at baseline. [c]Includes PHAROAH patients ($N = 4$), unless noted. [d]Does not include PHAROAH patients

At parent study baseline, all analyzed groups had mean FACIT-Fatigue scores below the general population norm of 43.6 [29] (Fig. 4), with a mean score of 34.1 in the total population. In patients from PEGASUS and PRINCE, mean FACIT-Fatigue scores were 31.5 and 36.9 at baseline, respectively. At 307-OLE entry, mean FACIT-Fatigue scores were approaching or above the general population norm in all populations. These scores were maintained through the 48-week cutoff.

A hemoglobin concentration > 12 g/dL was reached by 40.2% of evaluable patients in the total population at data cutoff (Table 3). In patients from PEGASUS and PRINCE, 36.8% and 46.4% had hemoglobin concentrations > 12 g/dL, respectively. Sex-specific hemoglobin normalization (i.e., ≥ 13.6 g/dL, male patients; ≥ 12 g/dL, female patients) occurred in 31.8% of the total population and in 31.6% of patients from PEGASUS and 28.6% from PRINCE. Normalization of LDH (i.e., ≤ 226 U/L [ULN]) was reached by 67.0% of evaluable patients in the total population. In patients from PEGASUS and PRINCE, 70.2% and 63.0% of patients had LDH normalization at the data cutoff in the 307-OLE, respectively.

In the total population, 83.2% of patients did not require a transfusion during the 307-OLE treatment period up to data cutoff (Fig. 5). Transfusion avoidance occurred during the 307-OLE in 76.6% of patients from PEGASUS and 90.0% of patients from PRINCE.



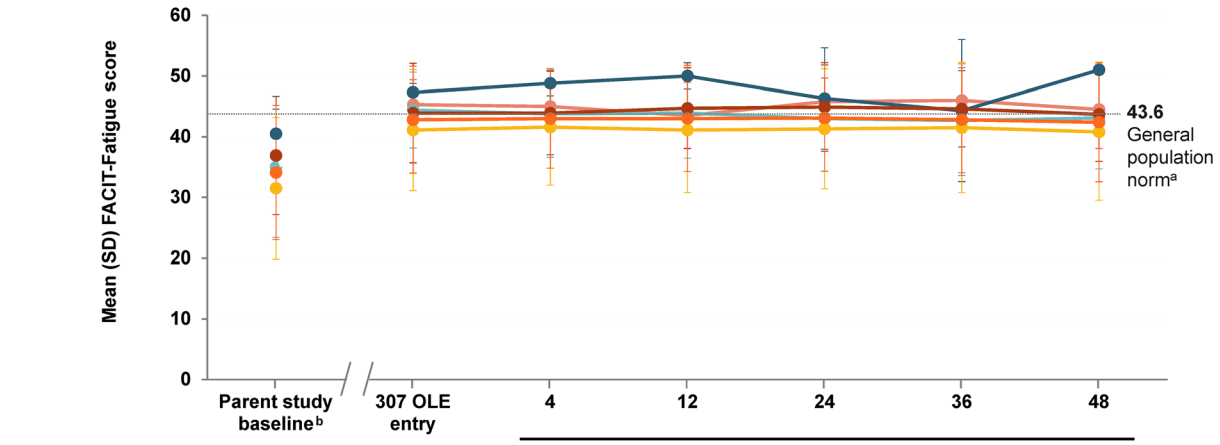
Median (IQR) LDH (U/L)							
PHAROAH (N=4)	NA	n=4 302 (200-340)	n=4 318 (153-734)	n=4 205 (166-220)	n=4 171 (144-216)	n=4 195 (169-301)	n=4 181 (163-237)
PALOMINO (N=4)	n=4 2585 (2098-3000)	n=4 186 (175-213)	n=4 187 (169-203)	n=4 191 (170-200)	n=4 206 (184-293)	n=4 200 (173-891)	n=4 204 (180-266)
PADDOCK (N=15)	n=15 2734 (1579-3315)	n=15 165 (147-343)	n=15 181 (124-322)	n=15 167 (131-386)	n=15 157 (144-346)	n=14 169 (146-322)	n=14 201 (156-434)
PEGASUS (N=64)	n=64 223 (194-271)	n=63 181 (143-227)	n=59 174 (153-217)	n=63 194 (157-240)	n=59 183 (147-253)	n=56 178 (156-216)	n=57 170 (148-215)
PRINCE (N=50)	n=50 2038 (1410-2658)	n=50 193 (152-283)	n=49 171 (140-210)	n=45 174 (149-236)	n=41 191 (163-221)	n=34 186 (160-428)	n=27 189 (156-234)
Total (N=137)[b]	n=133[c] 969 (227-2152)	n=136 184 (148-251)	n=131 174 (145-222)	n=131 185 (149-237)	n=123 185 (152-242)	n=112 180 (156-234)	n=106 180 (151-234)

Fig. 3 Concentrations of LDH at baseline of the PALOMINO, PADDOCK, PEGASUS, and PRINCE parent studies and from 307-OLE entry to week 48 in the total and parent study populations of patients with PNH. *IQR* interquartile range, *LDH* lactate dehydrogenase, *LLN* lower limit of normal, *NA* not available, *OLE* open-label extension, *PNH* paroxysmal nocturnal hemoglobinuria, *ULN* upper limit of normal. [a]Error bars for parent study baseline values were not included to maintain the scale. Patients in PALOMINO, PADDOCK, and PRINCE were complement inhibitor-naive at baseline. [b]Includes PHAROAH patients ($N = 4$), unless noted. [c]Does not include PHAROAH patients

Safety

Most patients (73.7%) in the total population ($N = 137$) reported AEs in the 307-OLE through data cutoff (Table 4). In the total population, 22 patients (16.1%) had AEs considered related to pegcetacoplan by the investigator. Fifteen patients (10.9%) reported AEs related to injection site reactions (ISRs). The most common TEAEs were hemolysis ($n = 23$, 16.8%), followed by fatigue ($n = 8$, 5.8%), and then upper respiratory tract infection, urinary tract infection, nasopharyngitis, headache, anemia, and injection site erythema ($n = 7$, 5.1% for all). No thrombotic events or meningococcal infections were reported.

Serious AEs were reported in 27 patients (19.7%) in the total population (none related to pegcetacoplan) (Table 4). The serious AE of hemolysis, the only serious AE reported by at least 5% of patients in the total population, occurred in 11 patients (8.0%). Three patients, two in PEGASUS and one in PRINCE, discontinued the study because of AEs; all three were due to hemolysis. One patient in PRINCE had a serious AE that was of severe intensity and led to death (sudden cardiac event on day 69 of the 307-OLE); this was deemed unrelated to pegcetacoplan.



Mean (SD) FACIT-Fatigue score							
PHAROAH (N=4)	NA	n=4 45.3 (4.11)	n=4 45.0 (3.46)	n=4 43.5 (5.45)	n=4 45.8 (3.86)	n=4 46.0 (5.35)	n=4 44.5 (6.45)
PALOMINO (N=4)	n=4 40.5 (4.04)	n=4 47.3 (1.50)	n=4 48.8 (2.06)	n=4 50.0 (2.16)	n=4 46.3 (8.34)	n=4 44.3 (11.70)	n=4 51.0 (0.82)
PADDOCK (N=15)	n=15 35.0 (11.59)	n=15 44.4 (6.23)	n=15 43.8 (7.18)	n=15 43.9 (7.42)	n=15 43.0 (8.72)	n=14 42.7 (8.62)	n=14 43.1 (8.39)
PEGASUS (N=64)	n=64 31.5 (11.66)	n=63 41.1 (9.97)	n=60 41.6 (9.57)	n=62 41.1 (10.28)	n=54 41.3 (9.89)	n=56 41.5 (10.73)	n=55 40.8 (11.27)
PRINCE (N=50)	n=48 36.9 (9.76)	n=49 43.9 (8.19)	n=49 43.9 (6.86)	n=44 44.7 (6.63)	n=40 44.9 (7.29)	n=33 44.6 (6.26)	n=27 43.7 (7.75)
Total (N=137)[c]	n=131[d] 34.1 (11.08)	n=135 42.8 (8.79)	n=132 43.0 (8.18)	n=129 43.0 (8.74)	n=117 43.1 (8.78)	n=111 42.8 (9.20)	n=104 42.4 (9.84)

Fig. 4 Scores for FACIT-Fatigue at baseline of the PALOMINO, PADDOCK, PEGASUS, and PRINCE parent studies and from 307-OLE entry to week 48 in the total and parent study populations of patients with PNH. *FACIT-Fatigue* Functional Assessment of Chronic Illness Therapy–Fatigue, *NA* not available, *OLE* open-label extension, *PNH* paroxysmal nocturnal hemoglobinuria, *SD* standard deviation. [a]Defined by Cella and colleagues [29]. A FACIT-Fatigue score increase ≥ 5 points is considered a clinically meaningful improvement [31]. [b]Patients in PALOMINO, PADDOCK, and PRINCE were complement inhibitor-naive at baseline. [c]Includes PHAROAH patients ($N = 4$), unless noted. [d]Does not include PHAROAH patients

In the 307-OLE, 23 patients (16.8%) a TEAE with the PT hemolysis (Table 4). One of these patients, who had high PNH disease activity and several other poorly controlled comorbidities, was considered an anomaly and was not included here. In the 22 patients with hemolysis who were analyzed, there were 25 events of hemolysis; 16 events were associated with a potential CAC, and for 9 events a potential CAC was not identified. Ten hemolysis events required transfusions. Patients had recovered per investigator judgment from 22 of the events at data cutoff. In all, 15 events were treated with an increase in pegcetacoplan dosage; one patient with a dosage increase had subsequent dosage reduction after a second hemolysis event. Three patients with hemolysis received ravulizumab or eculizumab during a hemolysis event, in addition to treatments for hemolysis, CACs, PNH, and/or comorbid conditions. Three of 22 patients with hemolysis events discontinued the study. Additional details are provided in the Supplementary Table.

Laboratory Result

At 307-OLE entry, more than 80% of patients in the total population had D-dimer normalization [30]. The percentage of patients with normalization remained steady through the 48-week data cutoff (Supplementary Figure).

Table 3 Percentage of patients with hemoglobin > 12 g/dL or normalization of hemoglobin or LDH at the week 48 visit of the 307-OLE in the total and parent study populations of patients with PNH

	Parent study					Total *N* = 137
	PHAROAH *N* = 4	PALOMINO *N* = 4	PADDOCK *N* = 15	PEGASUS *N* = 64	PRINCE *N* = 50	
Hemoglobin > 12 g/dL						
Evaluable patients[a]	*n* = 4	*n* = 4	*n* = 14	*n* = 57	*n* = 28	*n* = 107
n (%)	1 (25.0)	2 (50.0)	6 (42.9)	21 (36.8)	13 (46.4)	43 (40.2)
Sex-specific hemoglobin normalization[b]						
Evaluable patients[a]	*n* = 4	*n* = 4	*n* = 14	*n* = 57	*n* = 28	*n* = 107
n (%)	1 (25.0)	2 (50.0)	5 (35.7)	18 (31.6)	8 (28.6)	34 (31.8)
LDH normalization[c]						
Evaluable patients[a]	*n* = 4	*n* = 4	*n* = 14	*n* = 57	*n* = 27	*n* = 106
n (%)	3 (75.0)	3 (75.0)	8 (57.1)	40 (70.2)	17 (63.0)	71 (67.0)

LDH lactate dehydrogenase, *LLN* lower limit of normal, *OLE* open-label extension, *PNH* paroxysmal nocturnal hemoglobinuria, *ULN* upper limit of normal

[a]Patients with data available from the week 48 visit and no transfusions during the prior 60 days

[b]Hemoglobin normalization was defined as a hemoglobin concentration greater than or equal to the sex-specific LLN (13.6 g/dL, male patients; 12 g/dL, female patients)

[c]Normalization of LDH was defined as an LDH concentration less than or equal to the ULN (226 U/L) and no transfusions during the prior 60 days

DISCUSSION

Pegcetacoplan provided sustained, robust efficacy in patients with PNH through 48 weeks of the 307-OLE, with an AE profile that aligned with that established in pivotal trials, including no reports of thrombotic events or meningococcal infections during the 307-OLE at data cutoff. These findings demonstrate pegcetacoplan's long-term efficacy in all patients with PNH, regardless of C5 inhibitor experience. In C5 inhibitor-naive patients, pegcetacoplan sustained hematologic improvements for up to an additional 48 weeks. At data cutoff, 46.4% of evaluable patients from PRINCE had hemoglobin concentrations > 12 g/dL, 28.6% had sex-specific hemoglobin normalization, and 63.0% had LDH normalization, demonstrating marked and sustained improvements in hemolytic outcomes. Likewise, in C5 inhibitor-experienced patients with PNH, hemoglobin and LDH improvements persisted up to week 48 in the 307-OLE, with 36.8% of evaluable patients from PEGASUS having hemoglobin concentrations > 12 g/dL, 31.6% having sex-specific hemoglobin normalization, and 70.2% having LDH normalization. Although anemia persisted in approximately two-thirds of the patients in PEGASUS who received eculizumab, the improvement in hemoglobin concentrations remains noteworthy because all patients in PEGASUS had experienced residual anemia despite previous eculizumab treatment [24].

During the first 16 weeks of the PEGASUS trial, FACIT-Fatigue scores increased by nine points after 16 weeks of pegcetacoplan and decreased by three points with eculizumab, demonstrating clinically relevant reductions in fatigue (≥ 5 points) [24, 31] with pegcetacoplan. In a recent post hoc analysis of PEGASUS, these clinically meaningful fatigue improvements were shown to be extended to individual FACIT-Fatigue items; improvements with pegcetacoplan over eculizumab were clinically

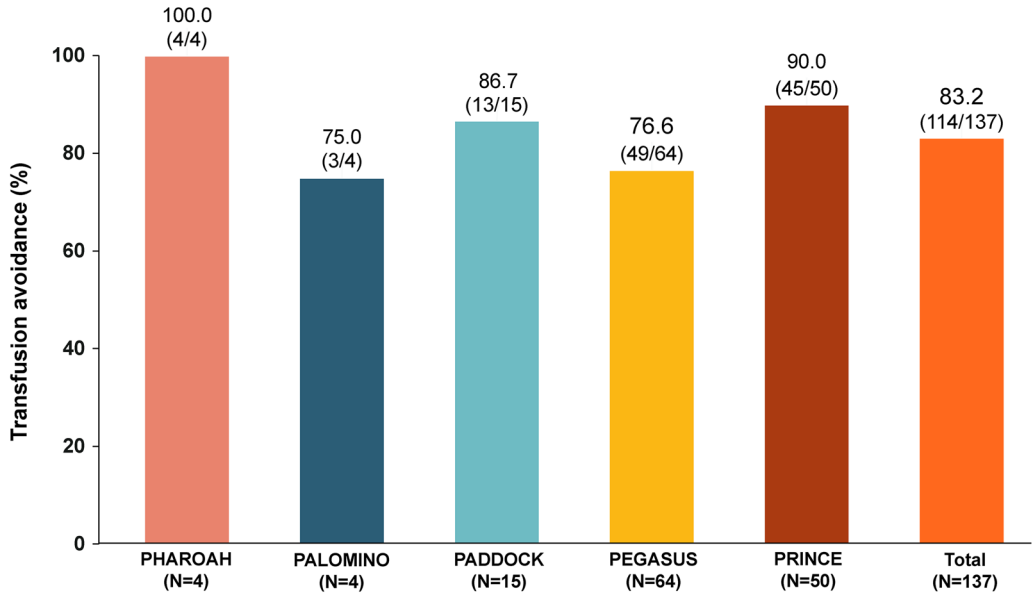


Fig. 5 Percentage of patients with transfusion avoidance[a] from 307-OLE entry to data cutoff in the total and parent study populations of patients with PNH. *OLE* open-label extension, *PNH* paroxysmal nocturnal hemoglobinuria. [a]Patients who avoided transfusion did not require a transfusion during the treatment period to the data cutoff (i.e., the earliest of week 48 of the 307-OLE or August 27, 2021)

meaningful for eight of 13 specific FACIT-Fatigue score items [32]. Through week 48 of the 307-OLE, overall fatigue reductions were maintained in the total population and in all parent study populations, including patients from PEGASUS who had a mean fatigue score at baseline of the parent study that indicated residual fatigue despite previous eculizumab treatment, demonstrating that long-term fatigue improvements are possible for patients who had suboptimal results with eculizumab. The need for such improvements was highlighted in a recent survey-based study, in which ongoing fatigue symptoms were reported by at least 74% of patients receiving a C5 inhibitor; corresponding results for patients receiving pegcetacoplan are not yet available [14].

Safety findings from the 48-week data cutoff of the 307-OLE support the favorable safety profile established for pegcetacoplan, with low incidence of hemolysis, no thrombotic events, and no meningococcal infections [24–28]. At the time of data cutoff, eight patients had withdrawn from the 307-OLE, including three who withdrew because of an adverse event (hemolysis in all cases) and one due to death from a sudden cardiac event considered unrelated to pegcetacoplan. PNH is characterized by hemolysis, which can occur as a result of CACs during complement inhibitor treatment. In the current study, 23 patients (16.8%) experienced a TEAE with the PT of hemolysis. Most hemolysis events were preceded by a potential CAC, and nearly all patients recovered. Management of acute hemolysis in this situation is not yet standardized, and close monitoring is warranted. Potential management options include increased dose of pegcetacoplan or supplemental treatment with a C5 inhibitor, with or without supportive care and transfusions, while addressing the driver(s) of hemolysis [33, 34]. A substudy of the 307-OLE, in which pegcetacoplan-treated patients with acute hemolysis receive intensive subcutaneous or intravenous administration of pegcetacoplan, is underway to assess the efficacy of intensive pegcetacoplan dosing [34]. As we await further data, it is essential to closely monitor patients for hemolysis events and to use the most recent findings to inform management decisions.

Though no thrombotic events were reported with pegcetacoplan in the 307-OLE, longer-

Table 4 Adverse events reported from 307-OLE entry through week 48 in the total and parent study populations of patients with PNH

n (%)	Parent study					Total *N* = 137
	PHAROAH *N* = 4	PALOMINO *N* = 4	PADDOCK *N* = 15	PEGASUS *N* = 64	PRINCE *N* = 50	
Any AE	4 (100.0)	2 (50.0)	12 (80.0)	60 (93.8)	23 (46.0)	101 (73.7)
AEs related to pegcetacoplan	0	1 (25.0)	3 (20.0)	13 (20.3)	5 (10.0)	22 (16.1)
AEs related to ISRs	0	1 (25.0)	2 (13.3)	10 (15.6)	2 (4.0)	15 (10.9)
TEAEs in ≥ 5% of patients in the total population						
Hemolysis	1 (25.0)	1 (25.0)	1 (6.7)	14 (21.9)	6 (12.0)	23 (16.8)
Fatigue	0	0	0	8 (12.5)	0	8 (5.8)
Upper respiratory tract infection	0	0	2 (13.3)	2 (3.1)	3 (6.0)	7 (5.1)
Urinary tract infection	1 (25.0)	0	1 (6.7)	3 (4.7)	2 (4.0)	7 (5.1)
Nasopharyngitis	0	0	1 (6.7)	5 (7.8)	1 (2.0)	7 (5.1)
Headache	0	0	1 (6.7)	5 (7.8)	1 (2.0)	7 (5.1)
Anemia	1 (25.0)	0	1 (6.7)	4 (6.3)	1 (2.0)	7 (5.1)
Injection site erythema	0	1 (25.0)	2 (13.3)	4 (6.3)	0	7 (5.1)
Any serious AE	1 (25.0)	1 (25.0)	3 (20.0)	16 (25.0)	6 (12.0)	27 (19.7)
Serious AEs related to pegcetacoplan	0	0	0	0	0	0
Serious AEs						
Hemolysis	0	1 (25.0)	0	9 (14.1)	1 (2.0)	11 (8.0)
Hemolytic anemia	0	0	1 (6.7)	0	1 (2.0)	2 (1.5)
COVID-19	0	0	0	2 (3.1)	0	2 (1.5)
Dengue fever	0	0	0	0	2 (4.0)	2 (1.5)
Anemia	0	0	0	1 (1.6)	0	1 (0.7)
Intravascular hemolysis	0	0	0	1 (1.6)	0	1 (0.7)
Ear infection	0	1 (25.0)	0	0	0	1 (0.7)
Infection	0	1 (25.0)	0	0	0	1 (0.7)
Pharyngitis	1 (25.0)	0	0	0	0	1 (0.7)
Respiratory tract infection	0	0	0	1 (1.6)	0	1 (0.7)
Urinary tract infection	0	0	1 (6.7)	0	0	1 (0.7)
Viral infection	0	0	0	1 (1.6)	0	1 (0.7)
Acute kidney injury	0	0	0	0	1 (2.0)	1 (0.7)
PNH	0	0	0	1 (1.6)	0	1 (0.7)

Table 4 continued

n (%)	Parent study					Total *N* = 137
	PHAROAH *N* = 4	PALOMINO *N* = 4	PADDOCK *N* = 15	PEGASUS *N* = 64	PRINCE *N* = 50	
Goiter	0	0	1 (6.7)	0	0	1 (0.7)
Food poisoning	0	0	1 (6.7)	0	0	1 (0.7)
Sudden cardiac death	0	0	0	0	1 (2.0)	1 (0.7)
Rib fracture	0	0	0	1 (1.6)	0	1 (0.7)
Cerebral infarction	0	0	0	1 (1.6)	0	1 (0.7)
Panic attack	0	0	0	1 (1.6)	0	1 (0.7)
AEs leading to study discontinuation[a]	0	0	0	2 (3.1)	1 (2.0)	3 (2.2)
AEs leading to death[b]	0	0	0	0	1 (2.0)	1 (0.7)

AEs were determined by the investigator

AE adverse event, *COVID-19* coronavirus disease 2019, *ISR* injection site reaction, *OLE* open-label extension, *PNH* paroxysmal nocturnal hemoglobinuria, *TEAE* treatment-emergent adverse event

[a]The three discontinuations were due to hemolysis

[b]Due to a sudden cardiac event that was deemed unrelated to pegcetacoplan

term studies could assess whether there is a decreased risk of thrombotic events with pegcetacoplan as there is with eculizumab in patients with PNH [11, 15, 35, 36]. The potential for increased meningococcal infections is a risk of disrupting the complement pathway [1]. No meningococcal infections were reported with pegcetacoplan during the 307-OLE up to week 48. Similarly, no meningococcal infections were reported in patients receiving ravulizumab or eculizumab through 2 years [10, 35, 37, 38]. Two of 195 patients in a phase 3 eculizumab extension reported meningococcal sepsis; however, both cases involved a serotype against which the patient had not been vaccinated [36]. Because of the proximal complement activity of pegcetacoplan, vaccinations against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B are required, in addition to vaccination against *Neisseria meningitidis*, before pegcetacoplan treatment [18, 19, 21]. No infections due to *S. pneumoniae* or *H. influenzae* were reported during the 307-OLE through data cutoff.

In addition, ISRs were reported in 10.9% of 307-OLE patients, which was a lower incidence than that observed with pegcetacoplan in PHAROAH [27], PALOMINO [28], PADDOCK [28], PRINCE [26], the active control portion of PEGASUS [24], and in patients who switched from eculizumab to pegcetacoplan during the open-label period of PEGASUS [25]. However, we acknowledge that ISRs are not a concern with oral treatment for PNH and that the dosing of pegcetacoplan may not be considered as convenient as a twice daily oral medication or less frequent infusions of a C5 inhibitor [20, 21, 39–41].

The current report of the 307-OLE 48-week data cutoff has limitations. The mixed patient population does not allow identification of patients who do or do not respond well to pegcetacoplan, although the responses demonstrate efficacy in patients with or without C5 inhibitor experience. Furthermore, this analysis was limited to singular outcomes rather than composite outcomes such as those developed by Risitano and colleagues [16]. This analysis was also limited by the heterogeneity of

pegcetacoplan dosages. Another limitation is that this is an ongoing study and data are variable until database lock. Clinical trial experience such as that reported here may not replicate real-world treatment patterns and outcomes.

Continuation of the extension to assess safety and efficacy over a longer period is ongoing. Further research could analyze data from prospective real-world studies [42], patient registries, or administrative claims to determine if findings are similar in other settings.

CONCLUSIONS

Pegcetacoplan sustained long-term improvements in hemoglobin and LDH concentrations and fatigue scores and reduced the transfusion burden in patients with PNH through up to 48 weeks of the 307-OLE, with an AE profile consistent with that in previous clinical trials. Pegcetacoplan maintained normalization of hematologic parameters, including hemoglobin concentrations, LDH concentrations, and FACIT-Fatigue. Long-term safety findings corroborate the favorable safety profile for pegcetacoplan established in previous clinical trials. These results support consistent safety and continued efficacy of pegcetacoplan, a novel PNH treatment option that inhibits earlier steps of complement pathway activation by targeting C3.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Michael Yeh is an employee of Apellis and holds stock options. Mohammed Al-Adhami was an employee of Apellis at the time of study completion. Christopher J. Patriquin reports relationships with Alexion, Apellis, Regeneron, Takeda, BioCryst, Swedish Orphan Biovitrum AB, Amgen, and Novartis. Andrija Bogdanovic reports relationships with Novartis, Takeda, Pfizer, and Apellis. Morag Griffin reports consultancy at Biocryst and Regeneron; honoraria from Alexion and Swedish Orphan Biovitrum AB; advisory board member at Novartis, Biocryst, Alexion, Amgen, and Swedish Orphan Biovitrum AB; and educational work sponsored by Apellis with unrestricted grant paid to Medscape. Richard J. Kelly has received research funding from Novartis, reports consultancy for Swedish Orphan Biovitrum AB, sat on advisory boards for Alexion, AbbVie, Amgen, Jazz,

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Ethical Approval. Parent study and 307-OLE protocols were designed and monitored in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki [26–30]. These protocols were approved by an institutional review board or independent ethics committee at each center. Each patient provided written informed consent before undergoing study-related procedures.

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