Long-term outcomes of pegcetacoplan treatment in patients with paroxysmal nocturnal hemoglobinuria and baseline hemoglobin levels greater than 10 grams per deciliter

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AIM

Evaluate **long-term efficacy** and **safety** of **pegcetacoplan** in **patients with paroxysmal nocturnal hemoglobinuria** (PNH) and **baseline hemoglobin (Hb) ≥10.0 g/dL** as part of an integrated analysis of the pivotal Phase 3 trials (PEGASUS, PRINCE) and the subsequent ongoing open-label extension study (NCT03531255) for **up to 3 years**.

INTRODUCTION

PNH is characterized by **complement-mediated hemolysis** and **increased risk of thrombosis**.[1] **Complement C5 inhibitors** (C5i) **reduce intravascular hemolysis** (IVH); however, **extravascular hemolysis** (EVH) **can become evident, resulting in persistent anemia**.[2]

Pegcetacoplan is the **first complement C3 and C3b inhibitor (C3i) approved by the EMA/FDA for the treatment of adults with PNH** and **targets IVH and EVH**.[3,4]

In Phase 3 trials, pegcetacoplan significantly increased Hb levels and improved other hematologic and clinical parameters in C5i-experienced (PEGASUS NCT03500549) and -naïve (PRINCE NCT04085601) adult patients with PNH. Mean Hb at baseline for both studies was <10 g/dL (mean Hb: 8.7 g/dL [PEGASUS], 9.1 g/dL [PRINCE]).

Long-term efficacy and safety of pegcetacoplan specifically in PNH patients with baseline Hb ≥10 g/dL have not been reported previously.

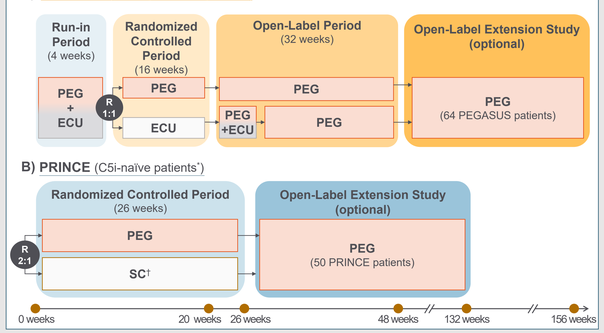
METHODS

Baseline was defined as time of pegcetacoplan initiation, regardless of when this occurred in the Phase 3 trials. **Adult PNH patients with baseline Hb ≥10.0 g/dL** at study entry or last assessment **before switching to pegcetacoplan from eculizumab (PEGASUS) or non-complement inhibitor supportive care (PRINCE) were included**.

Patients initially received pegcetacoplan **1080 mg subcutaneously twice weekly** but dose escalations to **once every 3 days or 3 times weekly** were permitted if a patient's **lactate dehydrogenase (LDH) level was greater than 2× upper limit of normal (ULN)**.

Long-term analyses were performed from baseline up to Weeks 132 **(2.5 years, PRINCE)** and 156 **(3 years, PEGASUS)**. Efficacy endpoints included changes from baseline in Hb, absolute reticulocyte count (ARC), LDH, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue). Safety was assessed from pegcetacoplan monotherapy initiation for up to 3 years.

Figure 1. Study design and key parameters in PEGASUS (A) and PRINCE (B)



* No C5i within 3 months of screening. † Patients in the PRINCE supportive care arm could escape to the pegcetacoplan arm before the end of the 26 weeks if they experienced a qualifying event of anemia or thrombosis.
C5i, complement 5 inhibitor; ECU, eculizumab; PEG, pegcetacoplan; R, randomization; SC, supportive care.

RESULTS

Baseline characteristics

- **At defined baseline**, **33 patients** (n=16 PEGASUS, n=17 PRINCE) had Hb ≥10.0 g/dL (data cutoff: 31/01/2023)
- **Table 1** summarizes the baseline characteristics
  - Mean (standard deviation [SD]) age was 47.0 (13.12) years, and 51.5% (71) were female

Table 1. Patient baseline characteristics

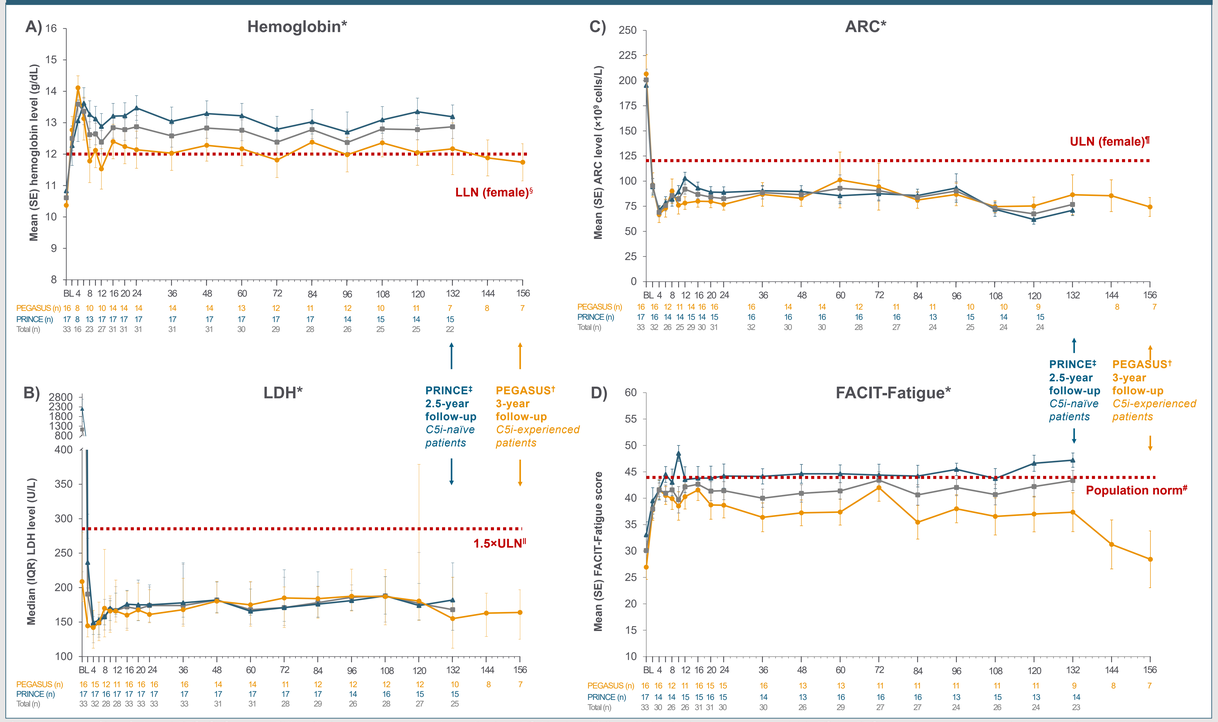
	PEGASUS (N=16)	PRINCE (N=17)	Total (N=33)
Age, years, mean (SD)	48.3 (13.34)	45.7 (13.19)	47.0 (13.12)
<65 years	13 (81.3)	16 (94.1)	29 (87.9)
≥65 to <75 years	3 (18.8)	1 (5.9)	4 (12.1)
Sex, n (%)			
Male	6 (37.5)	10 (58.8)	16 (48.5)
Female	10 (62.5)	7 (41.2)	17 (51.5)

SD, standard deviation.

Efficacy

- **At Week 2 after pegcetacoplan initiation**, **mean (standard error [SE]) Hb levels increased from 10.8 (0.2) g/dL at baseline to 12.3 (0.6) g/dL in PRINCE** and **from 10.4 (0.1) g/dL at baseline to 12.8 (0.4) g/dL in PEGASUS,** and levels remained **stable up to 2.5 (PRINCE)** and **3 years (PEGASUS)** (**Figure 2a**)
- Median **LDH decreased rapidly and stabilized below the ULN,** and **reductions in mean ARC to below ULN (female) were sustained** (**Figure 2b and c**)
  - At Week 2, median (interquartile range) LDH decreased from 2201.5 (1534.5, 2698.5) at baseline to 236.5 (199.5, 306.5) U/L in PRINCE and from 208.8 (179.8, 280.5) at baseline to 144.5 (128.5, 185.5) U/L in PEGASUS
  - At Week 2, mean (SE) ARC decreased from 195.2 (10.8) ×10^9 cells/L at baseline to 94.4 (8.2) ×10^9 cells/L in PRINCE and from 206.7 (19.2) ×10^9 cells/L at baseline to 96.3 (12.0) ×10^9 cells/L in PEGASUS
- **Improvements in hematologic parameters** translated into **rapid increases in mean FACIT-Fatigue scores**, approaching the general population norm by Week 4, and the **improved quality of life (QoL) was largely maintained long-term** (**Figure 2d**)

Figure 2. Hemoglobin (A), LDH (B), ARC (C), and FACIT-Fatigue score (D) in C5i-experienced (PEGASUS) and -naïve (PRINCE) patients with PNH and hemoglobin ≥10 g/dL treated with pegcetacoplan



* In the absence of transfusions. † PEGASUS enrolled PNH patients who remained anemic despite stable ECU treatment (≥3 months); patients were randomized 1:1 to ECU or PEG during the randomized controlled period through Week 16, after which ECU patients were switched to PEG monotherapy during the open-label period through Week 48. ‡ PRINCE enrolled PNH patients who were complement inhibitor-naïve and compared PEG to supportive care (excluding complement-inhibitors) through Week 26; supportive care patients had the option to escape to the PEG group if Hb decreased ≥2 g/dL from baseline levels or if they had a qualifying thromboembolic event. § Hemoglobin LLN (female): 12 g/dL. ‖ LDH normal reference range: 113–226 U/L. ¶ ARC, ULN (female): 120 ×10^9 cells/L. # FACIT-Fatigue score US population norm: 44.5 ARC, absolute reticulocyte count; C5i, complement 5 inhibitor; IQR, interquartile range; LDH, lactate dehydrogenase; LLN, lower limit of normal; PNH, paroxysmal nocturnal hemoglobinuria; SE, standard error; ULN, upper limit of normal.

Safety

- Safety events have been presented previously as part of the integrated analysis of the overall PRINCE and PEGASUS patients[6]
- **Table 2** summarizes adverse events (AEs) in patients with PNH and Hb ≥10 g/dL treated with pegcetacoplan. **In the up to 3 years of follow-up:**
  - Serious AEs were reported in 42.4% (14) of patients, none were pegcetacoplan-related
  - Serious treatment-emergent infections occurred in 24.2% (8) of patients, none of which were pegcetacoplan-related
  - **There were no cases of meningococcal infection**, and **3 cases of thrombosis**
  - **Two patients discontinued the study due to 3 AEs** (sepsis and diffuse large B-cell lymphoma [1 patient], and hemolysis [1 patient])
  - **There were no AEs leading to death**
  - **There were no new safety signals**

Table 2. Summary of adverse events in patients with PNH and Hb ≥10 g/dL

n (%)	PEGASUS 3-year follow-up (N=16)	PRINCE 2.5-year follow-up (N=17)	Total Up to 3 years of follow-up (N=33)
Any AE	16 (100)	17 (94.1)	32 (97.0)
AEs related to pegcetacoplan	*0 (0)*	*0 (0)*	*0 (0)*
Serious AEs	9 (56.3)	5 (29.4)	14 (42.4)
Serious AEs related to pegcetacoplan	*0 (0)*	*0 (0)*	*0 (0)*
AEs related to infusion site reaction	9 (56.3)	6 (35.3)	15 (45.5)
Treatment emergent infections	12 (75.0)	12 (70.6)	24 (72.7)
Treatment emergent infections related to pegcetacoplan	*0 (0)*	*0 (0)*	*0 (0)*
Serious treatment emergent infections	5 (31.3)	3 (17.6)	8 (24.2)
Serious treatment emergent infections related to pegcetacoplan	*0 (0)*	*0 (0)*	*0 (0)*
AEs leading to study discontinuation	**2 (12.5)**	**0 (0)**	**2 (6.1)***
AEs leading to death	**0 (0)**	**0 (0)**	**0 (0)**

AE, adverse event.

CONCLUSIONS

- The analysis demonstrated **sustained efficacy of pegcetacoplan in both C5i-experienced and -naïve patients with PNH and mild or moderate anemia (Hb ≥10 g/dL) at baseline**
- **Safety profile was consistent with reports from shorter treatment periods**
- **Patients with Hb ≥10 g/dL experienced swift and sustained improvements in hematologic parameters and enhanced QoL** with pegcetacoplan, showing these patients can also **benefit from pegcetacoplan treatment,** and underlining its significance as the sole C3i with substantial long-term data in this patient group

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ABBREVIATIONS: AEs, adverse events; ARC, absolute reticulocyte count; BL, baseline; C3i, complement 3 inhibitor; C5i, complement 5 inhibitor; ECU, eculizumab; EVH, extravascular hemolysis; Hb, hemoglobin; IVH, intravascular hemolysis; IQR, interquartile range; LDH, lactate dehydrogenase; LLN, lower limit of normal; PEG, pegcetacoplan; PNH, paroxysmal nocturnal hemoglobinuria; QoL, quality of life; R, randomization; SC, supportive care; SD, standard deviation; SE, standard error; ULN; upper limit of normal.

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