Early response in complement inhibitor naïve patients with paroxysmal nocturnal hemoglobinuria treated with pegcetacoplan in the Phase 3 PRINCE trial

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CONCLUSIONS

- This *post-hoc* analysis demonstrates a **high response rate to first-line usage of pegcetacoplan** as early as within 4 weeks of initiating treatment. **Patients benefited from immediate and sustained improvements in key hematological parameters**, including those required to enable symptom improvement (Hb) and demonstrate control of hemolysis (LDH).
- In patients in the control arm experiencing a Hb drop of ≥2 g/dL before pegcetacoplan initiation, **pegcetacoplan led to rapid hemolysis control** in most patients.
- These results provide **further evidence to support pegcetacoplan use in first-line treatment of adult PNH patients**.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by complement-mediated hemolysis, resulting in **increased thrombosis risk** and **substantial symptom burden**.[1]

Pegcetacoplan is a complement C3/C3b inhibitor approved in Europe, US and other countries to treat adult patients with PNH, providing **broad control of intravascular and extravascular hemolysis**.[2-5]

In **Phase 3 trials**, **pegcetacoplan demonstrated significant and sustained improvements in hematologic and clinical parameters** in complement 5 inhibitor (C5i)-experienced (PEGASUS) and -naïve (PRINCE) adult PNH patients.[6-8] Pegcetacoplan's efficacy and safety are **further supported by long-term and real-world data**.[9-15]

As real-world experience with pegcetacoplan in C5i-naïve patients evolves, there is a **need to further understand the role of pegcetacoplan in first-line treatment** to enable informed treatment decisions.

AIM

Determine early response rates and clinical outcomes in C5i-naïve patients receiving pegcetacoplan in the Phase 3 PRINCE trial

METHODS

In PRINCE (NCT04085601), **C5i-naïve adult PNH patients** were **randomized 2:1 to pegcetacoplan** (n=35) **or control** (supportive care; e.g., transfusions, corticosteroids and supplements) (n=18) through 26 weeks (**Figure 1**). **Eligible patients** had **lactate dehydrogenase (LDH)** levels **≥1.5× the upper limit of normal (ULN)** at screening.[6]

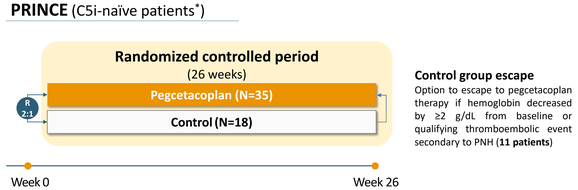
Per protocol, **control patients could escape to pegcetacoplan (escape patients) if they experienced hemoglobin (Hb) decrease ≥2 g/dL from study baseline, or a qualifying thromboembolic event** secondary to PNH.[6]

A ***post-hoc* analysis of PRINCE** was performed to **assess early response,** defined by achieving the following criteria within 4 weeks of pegcetacoplan initiation: **Hb increase ≥2 g/dL from baseline and/or Hb ≥12 g/dL, LDH <1.5×ULN, and no breakthrough hemolysis (BTH) events**, with complete response defined by achievement of all 3 criteria.

Response at Week 4 was evaluated for both patients randomized and escaped to pegcetacoplan, with baseline defined as pegcetacoplan initiation. Response at Week 26 was evaluated for patients randomized to pegcetacoplan.

Patients transfused prior to Week 4 were included as evaluable patients and deemed non-responders.

Figure 1. PRINCE study design[6]



* No C5i within 3 months of screening.
C5i, complement 5 inhibitor; PNH, paroxysmal nocturnal hemoglobiuria; R, randomization.

RESULTS

In total, **46 patients received pegcetacoplan during the randomized controlled period** (RCP) (pegcetacoplan patients, n=35; escape patients, n=11).

Within 4 weeks of pegcetacoplan treatment, **71.4% (25/35) of patients randomized to pegcetacoplan achieved complete response.** 71.4% (25/35) of patients achieved at least one of the defined Hb parameter(s) and 94.3% (33/35) achieved LDH <1.5×ULN (**Figure 2**).

Of the 10/35 patients randomized to pegcetacoplan who did not achieve early response at Week 4, **4/10 achieved complete response later** (median time to response 50.5 days [range 40-57]). One of the 10 patients without early response was lost-to-follow-up and had data missing; the patient was therefore defaulted as 'non-responder'.

Mean (standard deviation) Hb increased from 9.4 g/dL (1.4) at baseline **to 11.7 g/dL (1.8) at Week 4** in the patients randomized to pegcetacoplan (**Figure 2**).

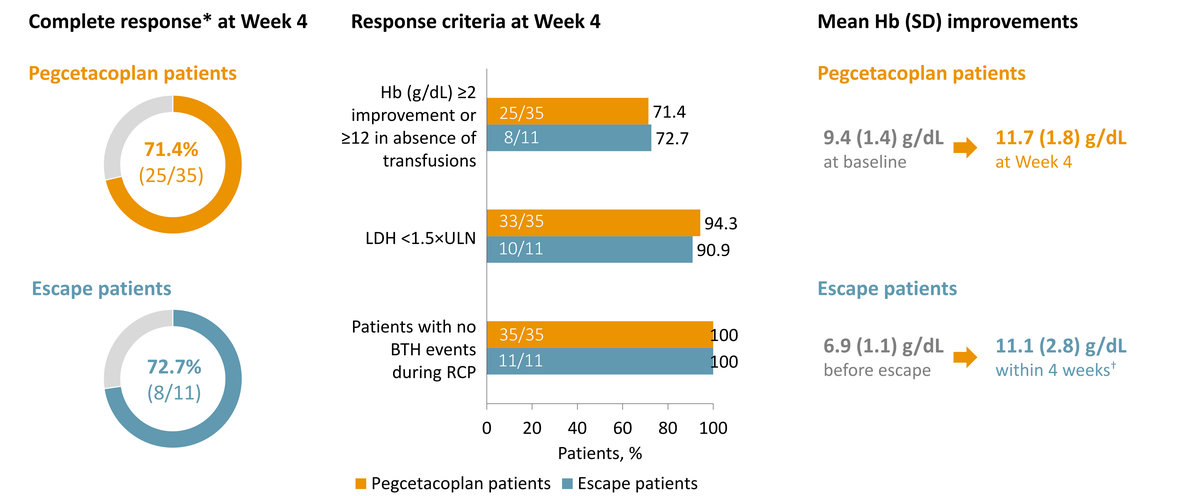
Hb and LDH improvements were sustained for the majority of patients randomized to pegcetacoplan **up to Week 26** (**Table 1**).

Within the **escape patient** group, **complete response was reached by 72.7% (8/11) of patients within 4 weeks** of pegcetacoplan initiation. 72.7% (8/11) of patients achieved at least one of the defined Hb parameter(s) and 90.9% (10/11) achieved LDH <1.5×ULN (**Figure 2**).

All 11 escape patients had LDH >1.5×ULN immediately prior to escape. **Mean (standard deviation) Hb increased** from 6.9 g/dL (1.1) at escape **to 11.1 g/dL (2.8) as highest mean within 4 weeks (Figure 2**). Two of 3 escape patients who did not reach complete response achieved a Hb increase ≥2 g/dL but were deemed non-responders due to receipt of transfusions immediately following escape prior to Week 4.

No BTH events occurred throughout the RCP in either groups (**Figure 2**).

Figure 2. Response at Week 4



* Complete response defined by achievement of all of the following: Hb improvement ≥2 g/dL from baseline and/or Hb ≥12 g/dL, LDH <1.5×ULN, AND no BTH events. † Highest value within 4 weeks.
BTH, breakthrough hemolysis; Hb, hemoglobin; LDH, lactate dehydrogenase; RCP, randomized controlled period; SD, standard deviation; ULN, upper limit of normal.

Table 1. Response at Week 26 for patients randomized to pegcetacoplan

	Pegcetacoplan patients (N=35)
Complete response*, n (%)	**22 (62.9)**
Hb (g/dL) ≥2 improvement or ≥12 in absence of transfusions, n (%)	23 (65.7)
LDH <1.5×ULN, n (%)	29 (82.9)
Patients with no BTH events during RCP, n (%)	35 (100)

* Complete response defined by achievement of all of the following: Hb improvement ≥2 g/dL from baseline and/or Hb ≥12 g/dL, LDH <1.5×ULN, AND no BTH events.
BTH, breakthrough hemolysis; Hb, hemoglobin; LDH, lactate dehydrogenase; RCP, randomized controlled period; ULN, upper limit of normal.

Safety

Pegcetacoplan was well tolerated. Most adverse events (AEs) were mild or moderate. Pegcetacoplan-related AEs occurred in 13 patients; none were considered to be serious by the investigators. No AEs led to discontinuation.[8]

For AEs of special interest, there were no serious infections (e.g., meningococcal infections), treatment-related sepsis, or PNH-relevant hemolytic events or thrombosis.[8]

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ABBREVIATIONS: BTH, breakthrough hemolysis; C5i, complement C5 inhibitor; Hb, hemoglobin; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RCP, randomized controlled period, ULN, upper limit of normal.

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