A benefit assessment of pegcetacoplan dose increase in the Phase 3 PEGASUS trial of PNH patients with difficult-to-control disease

PS1662

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CONCLUSIONS

- The **majority** (8 of 12) of evaluable PEGASUS patients who had **difficult-to-control disease benefited** from **their dose up-titration**
- These patients experienced **LDH decrease** with **no new safety signals**
- As per **pegcetacoplan's label**, **dose up-titration** from **1,080 mg BIW to Q3D** should be considered if a patient experiences **an LDH increase of >2× ULN**.*[3,4]

*In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks.[3,4]

INTRODUCTION

Paroxysmal nocturnal haemoglobinuria (PNH) is caused by **complement-mediated haemolysis**, resulting in **increased thrombosis risk** and **a substantial symptom burden**.[1] Complement C5 inhibitors (C5i) reduce intravascular haemolysis (IVH); however, residual IVH, extravascular haemolysis (EVH) and anaemia can persist in C5i-treated patients.[2]

Pegcetacoplan is a **complement C3/C3b inhibitor** providing **broad control** over **IVH** and **EVH**.[3,4]

In the Phase 3 PEGASUS trial of patients with persistent anaemia despite C5i treatment, pegcetacoplan demonstrated significant and sustained improvements in haematologic and clinical parameters versus C5i eculizumab.[5]

Pegcetacoplan is approved by the FDA for adult PNH patients and by the EMA for adult PNH patients with haemolytic anaemia.[3,4]

A **serum concentration threshold of 442 µg/mL** is required for **pegcetacoplan** to produce **90% of the proportional maximal change from baseline** (EC90) in **lactate dehydrogenase (LDH) improvement for C5i-treated** patients (data on file).

According to the pegcetacoplan EMA summary of product characteristics and US prescribing information, **pegcetacoplan dose** can be **increased from 1,080 mg twice weekly (BIW) to 1,080 mg every three days (Q3D)** when a patient experiences an LDH increase of >2× upper limit of normal (ULN)*, potentially indicating an **acute haemolysis event** that may be **pharmacokinetic** or **pharmacodynamic in nature**.[3,4]

*In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks.[3,4]

AIM

To assess the **benefits** of **pegcetacoplan dose up-titration** in PNH patients from the Phase 3 PEGASUS trial who had difficult-to-control disease.

METHODS

Patients from the Phase 3 PEGASUS trial (NCT03500549) who had a dose frequency increase from **1,080 mg BIW to 1,080 mg Q3D** were included in this *post-hoc* analysis **(Figure 1)**.

Reasons for dose up-titration and safety were examined in all patients who received Q3D dosing. The benefit of dose up-titration was evaluated in patients who received Q3D dosing for ≥30 days, where outcomes included stabilisation/increase in serum pegcetacoplan concentration, decrease in LDH, resolution of haemolysis and/or no occurrence of further haemolytic events, and study completion status **(Figure 1B)**.

RESULTS

Overall, **15 patients** in the PEGASUS study **had a dose up-titration to Q3D** and were included in this analysis:

- 10 patients had LDH levels >2× ULN prior to or at the time of dose up-titration
- **13 patients** due to **acute haemolysis**, **10 of whom had a potential complement-amplifying condition prior to haemolysis**
- 1 patient due to haemolytic anaemia
- 1 patient due to fatigue

12 of 15 patients* received Q3D dosing for ≥30 days and were further evaluated **(Table 1)**. Of these 12 patients, **8 benefited from pegcetacoplan dose up-titration and experienced an LDH decrease (Table 1)**.

* For 3/15 patients, pegcetacoplan dose was up-titrated to Q3D due to acute haemolysis; however, observation period on Q3D dosing was ≤30 days.

Among the 8 patients who benefited from pegcetacoplan Q3D dosing **(Table 1)**:

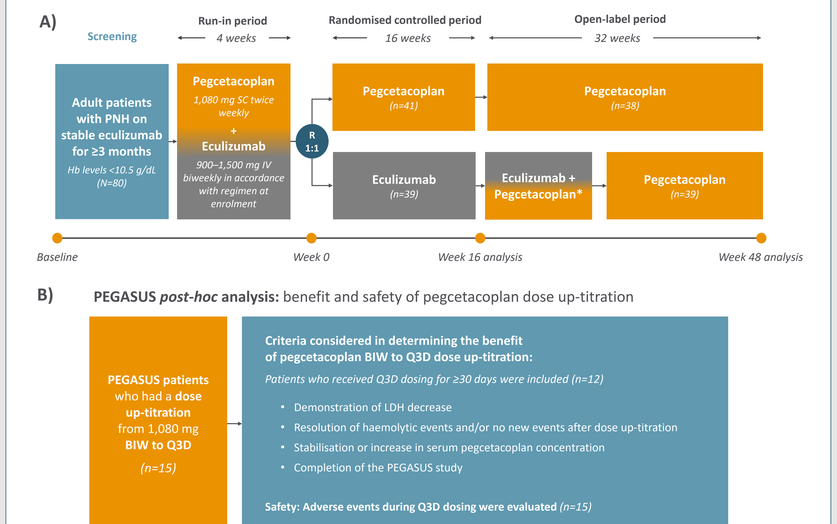
- **7 patients** experienced an **increase in haemoglobin (Hb)**
- **7 patients completed the PEGASUS trial**, **entered the open-label 307 extension study** (NCT03531255), and **continued Q3D dosing**
- For **6 patients**, **serum pegcetacoplan concentration** was <450 µg/mL during or before haemolysis and **increased to >500 µg/mL after dose up-titration**, indicating that **increased serum pegcetacoplan concentration with Q3D** dosing may have **contributed to improvements in LDH** and **Hb**, and **resolution of haemolysis**

No significant benefit was shown with Q3D dosing in 4 of 12 patients, in whom serum pegcetacoplan concentration reached >EC90 for LDH in 3 patients, suggesting that other factors may have influenced their response.

During or after dose up-titration, 13 of 15 patients (87%) experienced ≥1 treatment-emergent adverse event (TEAE).

TEAEs among patients who received Q3D dosing were consistent with those observed in the BIW group and the known pegcetacoplan safety profile.

Figure 1. PEGASUS study design (A) and *post-hoc* analysis on benefit and safety of pegcetacoplan dose up-titration (B)



PEGASUS ***post-hoc* analysis:** benefit and safety of pegcetacoplan dose up-titration

* Patients who received eculizumab during the 16-week randomised controlled period continued to receive eculizumab in addition to pegcetacoplan for the first 4 weeks of the open-label period. BIW, twice weekly; Hb, haemoglobin; IV, intravenous; PNH, paroxysmal nocturnal haemoglobinuria; Q3D, every 3 days; SC, subcutaneous.

Table 1. Characteristics of patients from PEGASUS who received pegcetacoplan Q3D dosing for ≥30 days (n=12)

Patient	Reason for dose up-titration to Q3D	Q3D duration (days)	LDH level following Q3D	Haemolysis status	Serum pegcetacoplan concentration following Q3D	Study completion status	Benefit demonstrated
1	Acute haemolysis *(potential CAC† of vaccination for 1st event)*	>30	Decreased	1st event resolved; 2nd event ongoing at the end of the study and resolved during extension study	Increased	Completed	**Yes**
2*	Fatigue	>30	Decreased	No haemolysis TEAE reported	Increased	Discontinued due to AML	**Yes**
3	Acute haemolysis *(potential CAC† of infection)*	>30	Decreased	Resolved	Increased	Completed	**Yes**
4	Acute haemolysis *(potential CAC† of URTI)*	>30	Decreased	Resolved	Increased	Completed	**Yes**
5	Acute haemolysis *(potential CAC† of diarrhoea)*	>30	Decreased	Event ongoing at the end of the study, and resolved during extension study	Increased	Completed	**Yes**
6	Acute haemolysis	>30	Decreased	Event ongoing at the end of the study, and resolved during extension study	Increased	Completed	**Yes**
7	Haemolytic anaemia‡ *(potential CAC† of bacterial infection)*	>30	Decreased	Resolved	Increased	Completed	**Yes**
8	Acute haemolysis *(potential CAC† of acute pancreatitis for 2nd event)*	>30	Decreased	Two events resolved; 3rd event ongoing at the end of the study, resolved during the extension study	Fluctuated	Completed	**Yes**
9	Acute haemolysis	>30	Remained high	Resolved	Decreased	Discontinued‖	No
10	Acute haemolysis *(potential CAC† of infection)*	>30	Fluctuated	Resolved	No change	Discontinued¶	No
11	Acute haemolysis *(potential CAC† of surgery, sepsis)*	>30	Fluctuated	Resolved	Decreased	Discontinued#	No
12	Acute haemolysis	>30§	Fluctuated	Resolved	No change	Completed	No

* For this patient, Q3D dosing was administered for ~1.5 months, which led to an increase in serum pegcetacoplan concentration and improved LDH level; treatment was discontinued due to acute myeloid leukaemia, which was deemed unrelated to pegcetacoplan.
† Potential CACs that occurred within 30 days of the haemolysis event were reviewed jointly by authors and analysis sponsors for a previous publication;[6] these were identified either as an AE reported by the investigator or inferred from records of concomitant medications.
‡ Patient 7 had an adverse event of haemolytic anaemia, which was not considered equivalent to events of acute haemolysis observed in other patients.[6]
§ Eculizumab was added on Day 148.
‖ Pegcetacoplan was discontinued due to acute haemolysis deemed possibly related to pegcetacoplan.
¶ Pegcetacoplan was discontinued due to acute haemolysis deemed not related to pegcetacoplan.
# Pegcetacoplan was discontinued due to intestinal ischaemia deemed possibly related to pegcetacoplan.
AML, acute myeloid leukaemia; CAC, complement-amplifying condition; LDH, lactate dehydrogenase; Q3D, every three days; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

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ABBREVIATIONS: AML, acute myeloid leukaemia; BIW, twice weekly; C5i, complement 5 inhibitor; CAC, complement-amplifying condition; EC90, 90% of the proportional maximal change from baseline (90% effective concentration); EMA, European Medicines Agency; EVH; extravascular haemolysis; FDA, Food and Drug Administration; Hb, haemoglobin; IV, intravenous; IVH, intravascular haemolysis; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; Q3D, every 3 days; SC, subcutaneous; TEAEs, treatment-emergent adverse events; ULN; upper limit of normal; URTI, upper respiratory tract infection.

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