Pegcetacoplan Rapidly Stabilizes Complement Inhibitor Naïve Patients with Paroxysmal Nocturnal Hemoglobinuria Experiencing Hemolysis with Acute Hemoglobin Decreases: PRINCE Trial Post Hoc Analysis

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OBJECTIVE

We aimed to conduct a post hoc time-aligned analysis evaluating the efficacy and safety of pegcetacoplan (PEG) in the patients who switched from the control arm to the PEG arm in the phase 3 PRINCE trial (NCT04085601)

CONCLUSIONS

- Pegcetacoplan treatment rapidly stabilized hemoglobin (Hb) in complement inhibitor-naïve patients experiencing a substantial Hb decrease. Lactate dehydrogenase (LDH) levels decreased to within normal range, suggesting control of intravascular hemolysis and prevention of extravascular hemolysis, and Hb levels increased
- The treatment effect of PEG on both LDH and Hb levels over time was largely similar between the PEG and rescue patients
- Pegcetacoplan represents a new effective therapeutic option with a favorable safety profile for patients with PNH

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CONTEXT

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired hematologic disease characterized by complement-mediated hemolysis and thrombosis[1-3]
- Pegcetacoplan (PEG) is the first approved C3 inhibitor for US adults with PNH[4] and EU adults with PNH who remain anemic despite stable C5 inhibitor treatment (ie, eculizumab or ravulizumab) for ≥3 months[5]
- Pegcetacoplan was superior to control treatment (supportive care only) for the co-primary endpoints of hemoglobin (Hb) stabilization and change in lactate dehydrogenase (LDH) levels from baseline at Week 26 in phase 3, randomized, open-label PRINCE trial (NCT04085601)[6]

METHODS

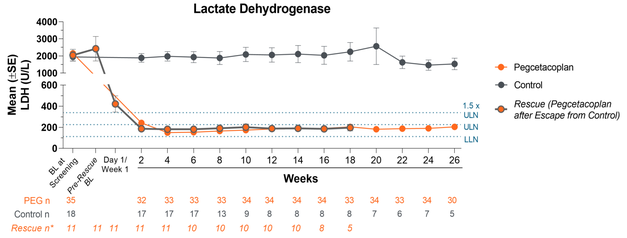
- PRINCE (conducted 2019–2021) enrolled 53 adults (≥18 years), who were complement inhibitor-naïve (no prior eculizumab/ravulizumab) and had LDH ≥1.5x the upper limit of normal (ULN; ≥339 U/L) and Hb below the lower limits of normal (males: ≤13.6 g/dL; females: ≤12.0 g/dL)
- Patients were randomized 2:1 to receive PEG or control treatment (supportive care only, including blood transfusions, corticosteroids, anticoagulants, and supplements [iron, folate, B12], in countries where complement inhibitors were not approved or widely available[6]) for 26 weeks
- Control (supportive care only) patients could escape to PEG treatment (rescue arm) with Hb decreases ≥2 g/dL from baseline
- A post hoc analysis was performed to time-align rescue patients with PEG patients to compare mean LDH and Hb changes over time
- Safety endpoints included incidences of adverse events (AEs)

RESULTS

Baseline Population & Characteristics

- PRINCE: N=53 (PEG n=35; control n=18; rescue n=11)
- Mean (range) age in years, was similar across treatment groups: PEG 42.2 (22–67); control 49.1 (20–74); rescue 51.0 (31–74)
- Median (range) years since PNH diagnosis was also similar: PEG 3.4 (0.1–27.0); control 4.7 (0.1–15.1); rescue 5.0 (0.3–15.1)

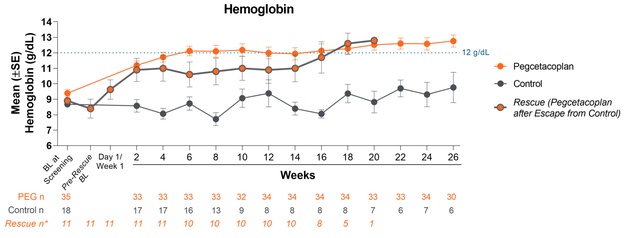
Post Hoc Time-Aligned Mean LDH Levels



PEG n	35			32	33	33	33	34	34	34	34	33	34	33	34	30
Control n	18			17	17	17	13	9	8	8	8	8	7	6	7	5
*Rescue n**	*11*	*11*	*11*	*11*	*11*	*10*	*10*	*10*	*10*	*10*	*8*	*5*				

*Rescue n is the number of patients from the control arm that switched to PEG when Hb decreased by ≥2 g/dL from baseline. Due to the time alignment based on treatment with PEG, this group does not have data out to Week 26.

Post Hoc Time-Aligned Mean Hb Levels

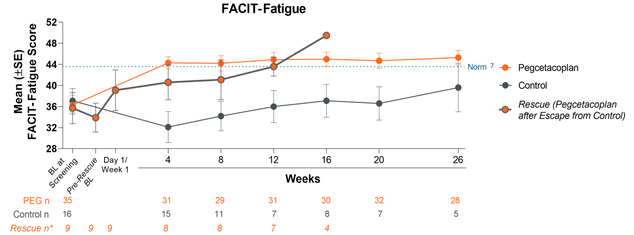


PEG n	35			33	33	33	33	32	34	34	34	34	33	33	34	30
Control n	18			17	17	16	13	9	8	8	8	8	7	6	7	6
*Rescue n**	*11*	*11*	*11*	*11*	*11*	*10*	*10*	*10*	*10*	*10*	*8*	*5*	*1*			

*Rescue n is the number of patients from the control arm that switched to PEG when Hb decreased by ≥2 g/dL from baseline. Due to the time alignment based on treatment with PEG, this group does not have data out to Week 26.

- Of the 11 patients in the rescue arm, 7 had a substantial increase in Hb level by Week 2 (mean Hb of rescue patients: 10.9 g/dL; PEG patients: 11.19 g/dL); 4 patients showed no change, potentially due to underlying bone marrow dysfunction (3 had a history of aplastic anemia)
- Three patients had a transfusion within 5 days of starting PEG treatment; 1 remained transfusion dependent after rescue and their Hb level did not change

Post Hoc Time-Aligned Mean FACIT-Fatigue Scores



PEG n	35		31	29	31	30	32	28
Control n	16		15	11	7	8	7	5
*Rescue n**	*9*	*9*	*8*	*8*	*7*	*4*		

*Rescue n is the number of patients from the control arm that switched to PEG when Hb decreased by ≥2 g/dL from baseline (2 patients in the control/rescue arm did not have available FACIT-Fatigue scores at baseline). Due to the time alignment with the PEG arm, this group does not have data out to Week 26.

Safety

	Overall PEG[a] (n=46)	Control[b] (n=18)
Any AE, n (%)	33 (71.7)	12 (66.7)
AEs Related to PEG	13 (28.3)	NA
Serious AEs, n (%)	4 (8.7)	3 (16.7)
Serious AEs Related to PEG	0	NA
AE by Severity, n (%)		
Mild or Moderate	29 (63.1)	10 (55.6)
Severe	4 (8.7)	2 (11.1)
TEAEs leading to PEG discontinuation, n (%)	0	--
Common TEAEs (>5%), n (%)		
Injection site reaction	14 (30.4)	0
Hypokalemia	6 (13.0)	2 (11.1)
Dizziness	5 (10.9)	0
Fever	4 (8.7)	0
Special interest AEs, n (%)		
Infections	9 (19.6)	5 (27.8)
Sepsis	0	0
Hypersensitivity	9 (19.6)	1 (5.6)
Hemolytic disorders	0	0
Thrombosis	0	0

[a] Overall PEG includes the original pegcetacoplan arm (n=35) and the rescue arm patients (n=11) that received PEG treatment upon escape from the control group to the PEG group
[b] Control includes any adverse event that occurred on or before escape to PEG; events occurring after escape to PEG were included in the overall PEG group

Abbreviations: PEG, Pegcetacoplan; Hb, Hemoglobin; LDH, Lactate dehydrogenase; PNH, Paroxysmal nocturnal hemoglobinuria; LLN, Lower limit of normal; ULN, Upper limit of normal; AEs, Adverse events; BL, Baseline; SE, Standard error; FACIT, Functional assessment of chronic illness therapy; TEAEs, Treatment emergent adverse events. Control treatment was supportive care only, (eg, transfusions, corticosteroids, anticoagulants, supplements [iron, folate, B12] in countries where complement inhibitors were not approved or widely available.