Pegcetacoplan PNH— C3 Deposition and PNH Clone Size in Pegasus

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EMPAVELI® (pegcetacoplan) injection for subcutaneous use, is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).[1]

RELEVANT PRESCRIBING INFORMATION

Clinical Pharmacology

Pharmacodynamics

In patients with PNH administered multiple doses of pegcetacoplan, the mean C3 concentration increased from 0.94 g/L at baseline to 3.80 g/L at Week 16 and sustained through Week 48 (Study APL2-302). In study APL2-308, the mean C3 concentration increased from 0.95 g/L at baseline to 3.56 g/L at Week 26.[1]

The percentage of PNH Type II + III RBCs increased from 66.2% at baseline to 93.9% at Week 16 and sustained through Week 48 (Study APL2-302). In Study APL2-308, the mean percentage of PNH Type II + III RBCs increased from 42.4% at baseline to 90.0% at Week 26.[1]

The mean percentage of PNH Type II + III RBCs with C3 deposition decreased from 17.8% at baseline to 0.20% at Week 16 and sustained through Week 48 (Study APL2-302). In Study APL2-308, the mean percentage of PNH Type II + III RBCs with C3 deposition decreased from 2.85% at baseline to 0.09% at Week 26.[1]

PEGASUS

Study Design

The efficacy and safety of pegcetacoplan were compared with the recombinant monoclonal anti-C5 antibody, eculizumab, in a Phase 3, randomized, open-label, controlled trial (PEGASUS, APL2-302, NCT03500549).[2] The study included 80 patients aged ≥18 years, with a confirmed diagnosis of PNH and hemoglobin <10.5 g/dL while on treatment with eculizumab at a stable dose for ≥3 months. Patients completed a run-in period of 4 weeks with pegcetacoplan plus eculizumab before 1:1 randomization to monotherapy with pegcetacoplan (41 patients, 1080 mg subcutaneously, twice weekly) or eculizumab (39 patients, continuing current dosing regimen) for 16 weeks.[2] During the 16-week randomized controlled period (RCP), 3 patients discontinued pegcetacoplan due to hemolysis. The remaining 77 patients entered the 32-week open label period (OLP; Week 17-48) and received pegcetacoplan monotherapy (1080 mg subcutaneously twice weekly).[3] Those patients who received eculizumab in the RCP received pegcetacoplan in addition to eculizumab for 4 weeks (Weeks 17-20) before starting pegcetacoplan monotherapy.

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Study Endpoints

The primary endpoint was change in hemoglobin level from baseline to Week 16 and then at Week 48.[2,3] Key secondary endpoints were transfusion avoidance, absolute reticulocyte counts, lactate dehydrogenase (LDH) levels, Functional Assessment of Chronic Illness Therapy-fatigue (FACIT-f) score, and treatment-emergent adverse events (TEAEs).

Pharmacodynamic endpoints analyzed included C3d deposition on red blood cells (RBC) and clone size of Type II + III PNH RBCs.[2,3]

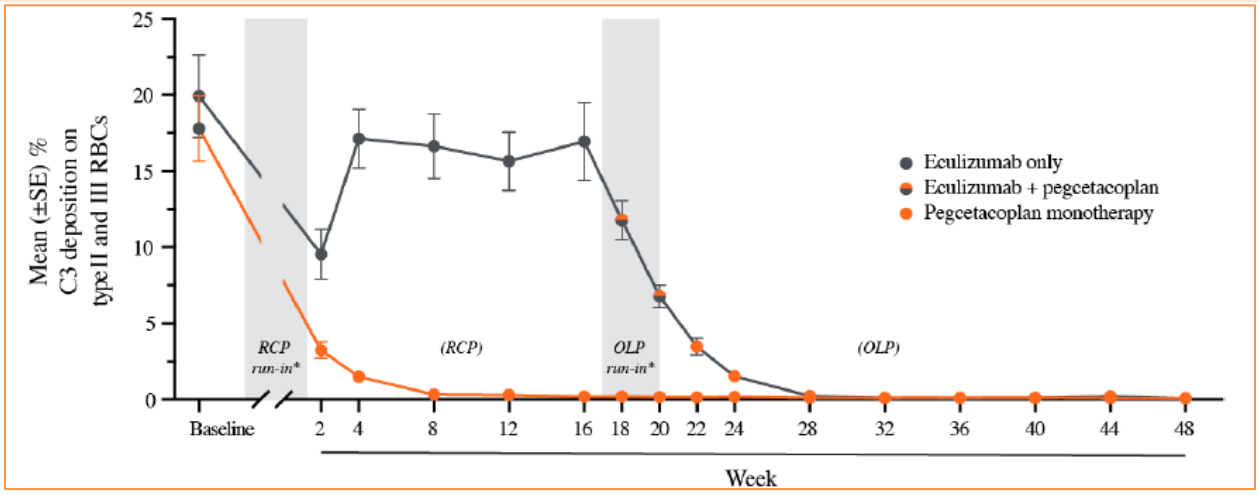
C3 Loading and PNH Clone Size During RCP

In the pegcetacoplan group, the proportion of C3 loading decreased and the proportion of Type II + III PNH red blood cells (RBCs) increased.[2] The mean C3 deposition on Type II + III PNH RBCs decreased from a baseline value of 17.7% to 0.2% at Week 16 with pegcetacoplan vs 19.8% to 16.9% for eculizumab. The mean percentage of Type II + III PNH RBCs increased from 66.8% at baseline to 93.9% at Week 16 in the patients who received pegcetacoplan vs a decline from 72.9% to 62.6% for eculizumab **(Table 1)**.[2]

C3 Loading and PNH Clone Size During OLP

Pegcetacoplan treatment decreased C3 deposition on Types II and III PNH RBCs and increased PNH RBC clone size (**Figure 1. Table 1**).[3] At Week 48, the summed mean of PNH RBC clonal distribution (% PNH Type II + III PNH RBCs) represented nearly 90% of overall PNH RBCs for patients in both the pegcetacoplan-to-pegcetacoplan and eculizumab-to-pegcetacoplan groups. Pegcetacoplan-to-pegcetacoplan patients maintained reduction through 48 weeks and eculizumab-to-pegcetacoplan patients showed decreases in C3 deposition after switching to pegcetacoplan at Week 18 on Types II and III PNH RBCs.[3]

Figure 1. C3 deposition on type II and type III PNH red blood cells[3]



Pegcetacoplan run-in periods: 1) before randomization, for both PEG-to-PEG and ECU-to-PEG treatment arms; and 2) before the open-label period, for the ECU-to-PEG treatment arm only. OLP=open-label period. PNH=paroxysmal nocturnal hemoglobinuria. RBC=Red blood cell. RCP=randomized controlled period. SE=Standard error

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Table 1. PNH Clone Size of Type II + III PNH Red Blood Cells[3,4]

	PEG-to-PEG			ECU-to-PEG		
	Baseline n=41	**Week 16** n=32	**Week 48** n=21	**Baseline** n=39	**Week 16** n=37	**Week 48** n=18
Clone size: % Type II + III PNH RBCs, Mean (SD)	66.8 (26.5)	93.9 (6.4)	88.8 (18.9)	72.9 (25.8)	62.6 (26.0)	92.7 (13.9)

SD=standard deviation; PEG=pegcetacoplan; ECU=eculizumab; RBCs=red blood cells.

Safety of Pegcetacoplan vs Eculizumab During RCP

The most common adverse events (AE) in the pegcetacoplan and eculizumab groups, respectively were injection site reactions (37% vs 3%), diarrhea (22% vs 3%), breakthrough hemolysis (10% vs 23%), headache (7% vs 23%), and fatigue (5% vs 15%).[2] Reports of serious AEs were similar for both treatments: 7 of 41 patients (17%) in the pegcetacoplan group and 6 of 39 patients (15%) in the eculizumab group.

Safety of Pegcetacoplan During 32-Week OLP

The safety profile of pegcetacoplan was consistent with previously reported data throughout the study. Of 77 pegcetacoplan monotherapy-treated patients, 18 experienced a serious AE; 4 of the serious AEs (6%) were considered as related to pegcetacoplan.[3] The most common adverse events reported throughout the 48 weeks for the pegcetacoplan-to-pegcetacoplan and eculizumab-to-pegcetacoplan, respectively were nasopharyngitis (16% vs 15%), injection site reactions (18% vs 33%), hemolysis (18% vs 21%), and diarrhea (13% vs 13%).

REFERENCES

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3. Peffault de Latour R, Szer J, Weitz IC, et al. Pegcetacoplan versus eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PEGASUS): 48-week follow-up of a randomised, open-label, phase 3, active-comparator, controlled trial. *Lancet Haematol*. 2022;9(suppl):e648-e659.
4. Peffault de Latour R, Szer J, Weitz IC, et al. Forty-eight week efficacy and safety of pegcetacoplan in adult patients with paroxysmal nocturnal hemoglobinuria and suboptimal response to prior eculizumab treatment. Abstract and presentation presented at: 26th European Hematology Association (EHA) Annual Meeting; June 9-17, 2021: Virtual.