Rapid Time to a Clinically Meaningful Response in FACIT-Fatigue Scores with Pegcetacoplan in Patients with Paroxysmal Nocturnal Hemoglobinuria: A Kaplan-Meier Analysis from the PEGASUS Trial

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OBJECTIVE

This post hoc analysis aims to compare pegcetacoplan to eculizumab in time to achieve a clinically meaningful response in FACIT-Fatigue score through Week 16 using the Kaplan-Meier estimate and log-rank test. The outcome measures were 1) ≥3 point and ≥5-point improvement in FACIT-Fatigue total score, and 2) FACIT-Fatigue total score normalization

CONCLUSIONS

- Overall, patients treated with pegcetacoplan showed a significantly higher probability of displaying rapid, clinically meaningful improvements in FACIT-Fatigue total scores
- Pegcetacoplan-treated patients had a significantly higher probability of demonstrating FACIT-Fatigue total score normalization than eculizumab-treated patients

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References: 1. Parker C, et al. *Blood.* 2005;106(12):3699–709. 2. Risitano A, et al. *Biologics: Targets & Therapy.* 2008;2(2):205-255. 3. Hillmen P, et al. *N Engl J Med* 1995; 333:1253-1258. 4. Schrezenmeier H, et al. *Haematologica.* 2014;99(5):922-929. 5. *Cella D, et al. J Pain Symptom Manage. 2002;24(6):547-561. 6.* Cella, et al. Blood. 2021:138(Supplement 1):1952-1952. 7. Cella, et al. Cancer. 2002;94(2):528-538

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CONTEXT

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, life-threatening disease characterized by chronic complement-mediated hemolysis causing anemia and fatigue[1,2]
- Pegcetacoplan (PEG) is the first approved C3 inhibitor that demonstrated superiority over eculizumab in improving hemoglobin levels in adults with PNH (phase 3 PEGASUS trial)[3]
- Fatigue is the most common and burdensome patient-reported symptom associated with PNH[4]. Thus, measuring fatigue is an important clinical consideration in choosing a treatment modality from both, a patient and clinician perspective

METHODS

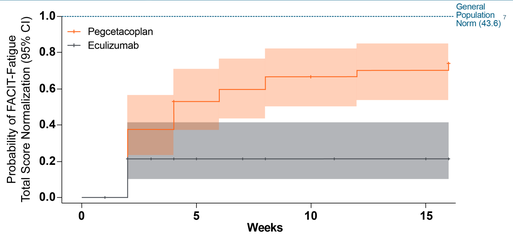
- PEGASUS (NCT03500549) enrolled a total of 80 adult patients diagnosed with PNH (≥18yrs) that remained anemic (hemoglobin <10.5 g/dL) despite stable eculizumab (ECU) treatment for ≥3 months[3]
- Patients completed a 4-week eculizumab + pegcetacoplan run-in period followed by 1:1 randomization to pegcetacoplan (n=41; 1080 mg subcutaneously twice weekly) or eculizumab (n=39) through Week 16
- Fatigue was measured through Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, which is a 5-point Likert scale instrument (scores 0–52). A ≥3-point[5] and a ≥5-point[6] improvement in the FACIT-Fatigue total score is considered clinically meaningful in PNH
- FACIT-Fatigue normalization was defined as total score of ≥43.6 (general population norm)[7]
- The post hoc analysis used the log-rank test and Kaplan-Meier curve to calculate the FACIT-Fatigue total score normalization, as well as the clinically-relevant significant improvement of the FACIT-Fatigue total score
- Patients who received red blood cell transfusions during the 16-week study period were censored at the time of the transfusion

RESULTS

Baseline Population & Characteristics

	Pegcetacoplan	Eculizumab
Population Size, (N)	41	39
Overall age in years, Mean (range)	50.2 (19-81)	47.3 (23-78)
Proportion of female patients, n (%)	27 (66.0)	22 (56.0)
Years since PNH diagnosis, Median (range)	6.0 (1-31)	9.7 (1-38)

FACIT-Fatigue Total Score Normalization



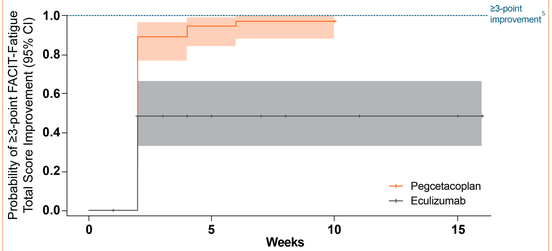
The propability of 1.0 is shown as a 100% probability of seeing a normalized total FACIT-Fatigue score. 95% confidence intervals are presented as a faded color indicating upper and lower bounds relative to probability of pegcetacoplan or eculizumab to normalize the total FACIT-Fatigue score.

As soon as Week 2, patients treated with PEG have a higher probability (37.50%) to achieve normalized FACIT-fatigue total scores compared to patients treated with ECU (21.43%)

Log rank test p-value	Pegcetacoplan n/N[a,b]	Eculizumab n/N[a,b]
0.0086[c]	23/32	6/29

[a](n) number of patients with improvements within 16 weeks / (N) number of patients in the analysis cohort
[b]Patients with a baseline score of ≥43.6 scores at baseline were excluded from this analysis as they already were at or above the population norm at baseline
[c]p-value <0.05 indicates a significantly higher rate of improvement in the item-level measure for PEG compared to ECU after patients were censored for red blood cell transfusions

≥3-point Improvement



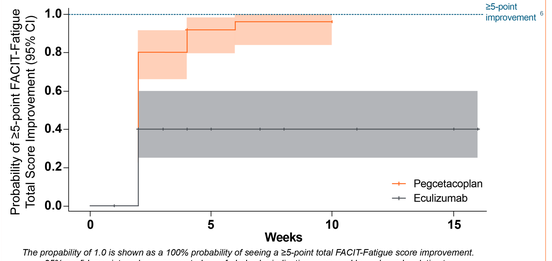
The propability of 1.0 is shown as a 100% probability of seeing a ≥3-point total FACIT-Fatigue score improvement. 95% confidence intervals are presented as a faded color indicating upper and lower bounds relative to probability of pegcetacoplan or eculizumab to reach a ≥3-point improvement in the total FACIT-Fatigue score.

As soon as Week 2, patients treated with PEG have a higher probability (89.19%) of ≥3-point FACIT-Fatigue total score improvement compared to patients treated with ECU (48.48%)

Log rank test p-value	Pegcetacoplan n/N[a,b]	Eculizumab n/N[a,b]
<0.0001[c]	36/37	16/34

[a](n) number of patients with improvements within 16 weeks / (N) number of patients in the analysis cohort
[b]Patients with a baseline score ≥49 were excluded from this analysis, as they could not reach a ≥3-point improvement
[c]p-value <0.05 indicates a significantly higher rate of improvement in the item-level measure for PEG compared to ECU after patients were censored for red blood cell transfusions

≥5-point Improvement



The propability of 1.0 is shown as a 100% probability of seeing a ≥5-point total FACIT-Fatigue score improvement. 95% confidence intervals are presented as a faded color indicating upper and lower bounds relative to probability of pegcetacoplan or eculizumab to reach a ≥5-point improvement in the total FACIT-Fatigue score.

As soon as Week 2, patients treated with PEG have a higher probability (80.00%) of ≥5-point FACIT-Fatigue total score improvement compared to patients treated with ECU (40.00%)

Log rank test p-value	Pegcetacoplan n/N[a,b]	Eculizumab n/N[a,b]
<0.0001[c]	33/35	12/31

[a](n) number of patients with improvements within 16 weeks / (N) number of patients in the analysis cohort
[b]Patients with a baseline score ≥47 were excluded from this analysis, as they could not reach a ≥5-point improvement
[c]p-value <0.05 indicates a significantly higher rate of improvement in the item-level measure for PEG compared to ECU after patients were censored for red blood cell transfusions

Safety

	Pegcetacoplan n=41	Eculizumab n=39		Pegcetacoplan n=41	Eculizumab n=39
Any AE, n (%)	36 (87.8)	36 (92.3)	**Special interest AEs,** n (%)		
PEG-related	14 (34.1)	--	Injection site reactions	15 (36.6)	1 (2.6)
Serious AEs, n%	7 (17.1)	5 (12.8)	Infections	12 (29.3)	11 (28.2)
PEG-related	1 (2.4)	--	Sepsis	0	0
TEAEs leading to PEG discontinuation, n (%)	2 (4.9)	--	Hypersensitivity	5 (12.2)	2 (5.1)
			Hemolytic disorders	5 (12.2)	14 (35.9)
			Thrombosis	0	0

Abbreviations: AE(s), adverse event(s); ECU, eculizumab; FACIT, Functional Assessment of Chronic Illness Therapy; ISRs, injection site reactions, PEG, pegcetacoplan; PNH, paroxysmal nocturnal hemoglobinuria; RCP, randomized controlled period; TEAE, treatment emergent adverse event.