

Efficacy and Safety at 48 Weeks of Pegcetacoplan in Adult Paroxysmal Nocturnal Hemoglobinuria Patients with Suboptimal Response to Prior Eculizumab Treatment

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CONCLUSIONS

- ✓ **Efficacy:**
 - ✓ Pegcetacoplan-treated patients with paroxysmal nocturnal hemoglobinuria (PNH) experienced sustained improvements related to disease characteristics (hemoglobin, LDH, ARC, freedom from transfusions) through 48 weeks of treatment
 - ✓ The treatment-effect of PEG on hemoglobin levels over time was similar between PEG-to-PEG and ECU-to-PEG groups, suggesting PEG represents a new effective treatment option for adult patients with PNH
- ✓ **Safety:**
 - ✓ The safety profile of pegcetacoplan demonstrated a favorable risk-benefit balance
 - ✓ No major safety signals have emerged (in particular in terms of infectious and/or auto-immune complications), except for 5 cases of breakthrough hemolysis requiring treatment discontinuation (only 2 of which were deemed definitely related to pegcetacoplan)

These results suggest that pegcetacoplan can control intravascular and prevent extravascular hemolysis in adult patients with PNH and may represent a promising new therapeutic option for the disease.

INTRODUCTION

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and potentially life-threatening disease that is characterized by hemolysis and thrombosis²
- Treatment for this complement-mediated disease relies predominantly on C5-inhibitors, such as eculizumab (ECU), which prevent intravascular hemolysis, but they do not block C3-mediated extravascular hemolysis³
- Pegcetacoplan (PEG), an inhibitor of the C3 complement pathway that controls intravascular hemolysis (IVH) and prevents extravascular hemolysis (EVH)², was recently approved in the US for use in adults with PNH by the Food and Drug Administration

AIMS

Report on the efficacy and safety of PEG and results from a post hoc time-adjusted analysis based on start of PEG dosing

METHODS

Patients and Study Design

- PEGASUS (NCT03500549) was a phase 3, randomized, multi-center, open-label, active-comparator controlled trial

Figure 1. Study Timeline

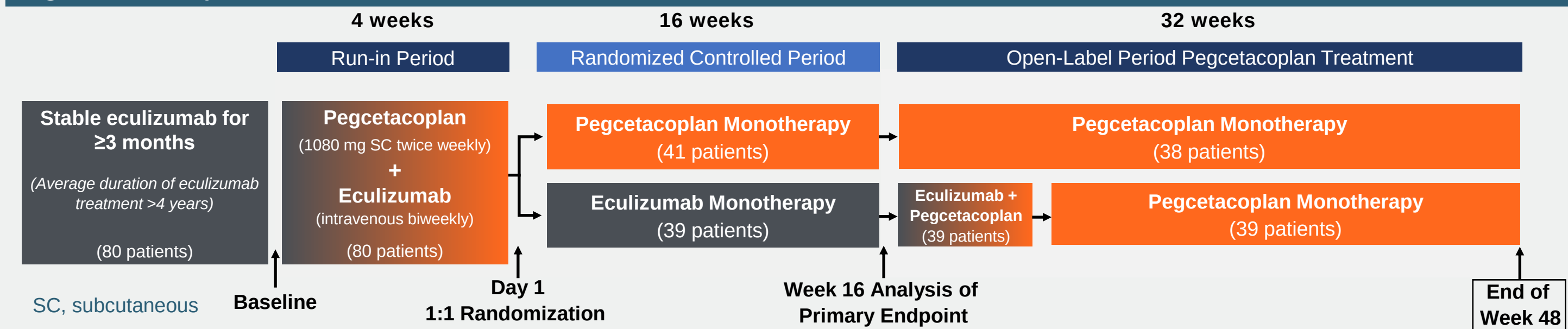


Table 1. Study Design

Population	Patients ≥18 years of age with PNH and hemoglobin <10.5 g/dL despite stable treatment with eculizumab (≥3 months)
Primary Endpoint	Change from baseline in hemoglobin level at Week 16
Week 48 Endpoints	
Efficacy Endpoints	• Change from baseline in hemoglobin levels, LDH levels, ARC, and FACIT-Fatigue score • Freedom from transfusions
Safety Endpoints	Incidence and severity of TEAEs
Treatment Groups	• PEG-to-PEG: Patients received pegcetacoplan during the randomized controlled period and continued through Week 48 of the open-label period • ECU-to-PEG: Patients received eculizumab during the randomized controlled period and switched to pegcetacoplan during the open-label period after a 4-week run-in
Post Hoc Endpoint	Timepoints were time adjusted to compare changes in endpoints based on the duration of PEG dosing (ECU-to-PEG: Week 16 to Week 48; PEG-to-PEG: Week -4 to Week 28)

ARC, absolute reticulocyte count; ECU, eculizumab; FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; PEG, pegcetacoplan; PNH, paroxysmal nocturnal hemoglobinuria; TEAEs, treatment-emergent adverse events

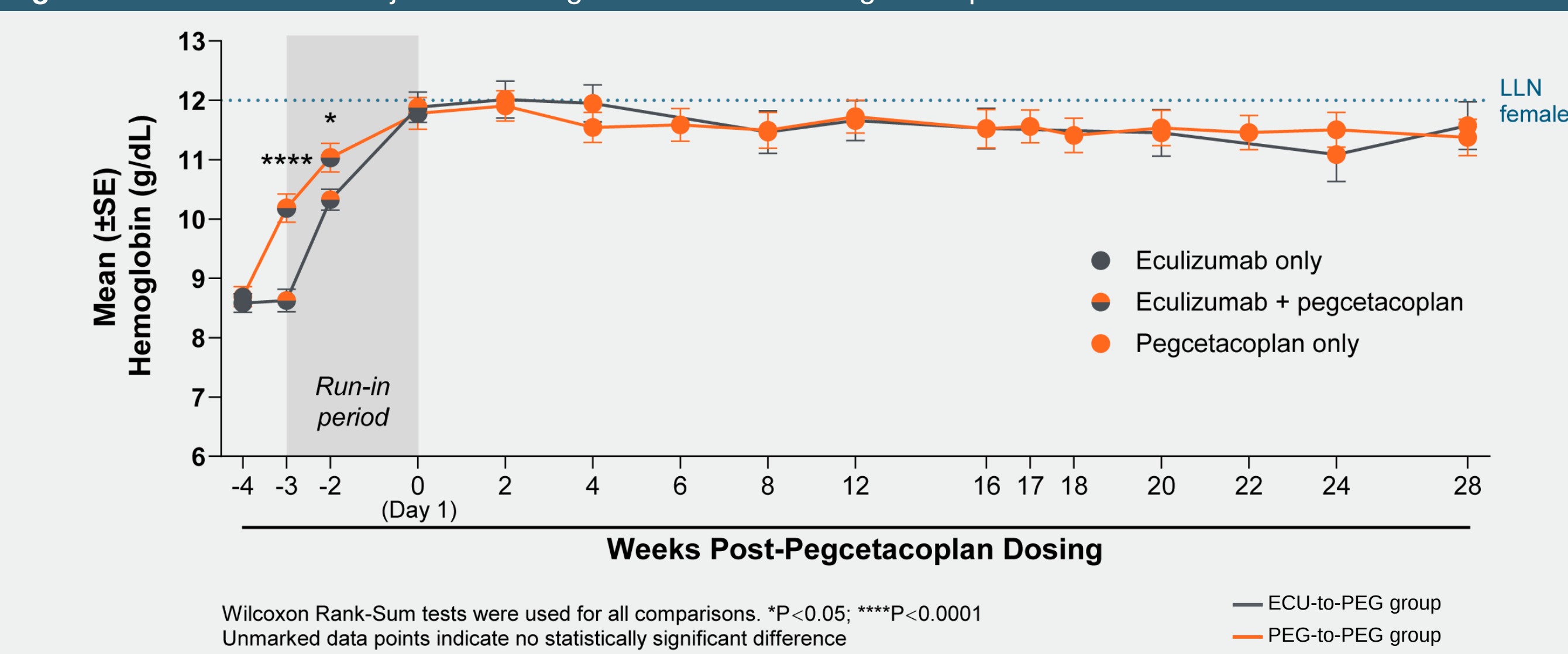
RESULTS

Hemoglobin Levels: Post Hoc Time Adjusted

- In the first and second weeks of the run-in period, the time adjusted average hemoglobin levels of the PEG-to-PEG group showed a significantly higher increase compared to the ECU-to-PEG group (p <0.0001^a and p <0.05^a, respectively) (PEG-to-PEG: Week -3 and -2; ECU-to-PEG: Week 17 and 18) (**Fig. 2**)
- After the run-in period, there were no significant differences between the time adjusted hemoglobin levels of the ECU-to-PEG group compared to 28 Weeks post-PEG dosing (PEG-to-PEG: Week 28, ECU-to-PEG: Week 48) (**Fig. 2**)

^aUncorrected/nominal p-value

Figure 2. Post Hoc Time Adjusted Hemoglobin Levels with Pegcetacoplan Treatment

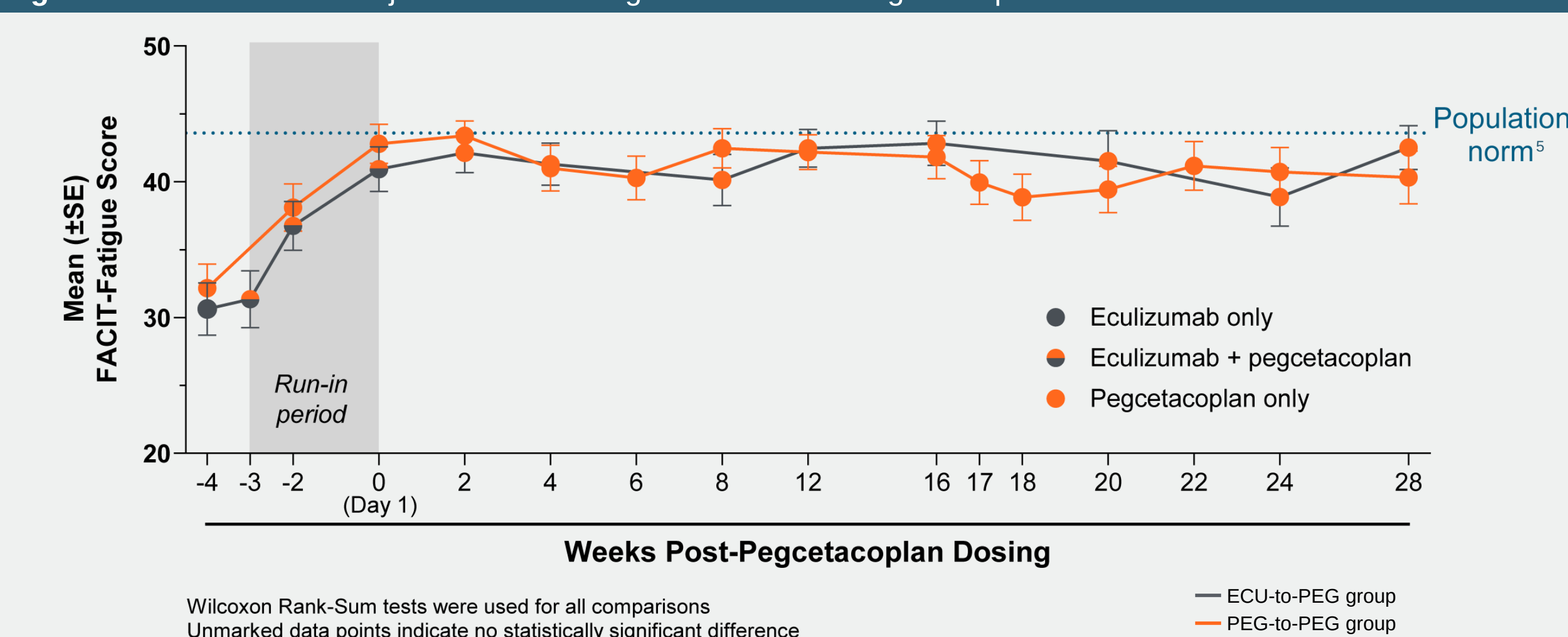


ECU, eculizumab; LLN, lower limit of normal; PEG, pegcetacoplan; SE, standard error

FACIT-Fatigue Scores: Post Hoc Time Adjusted

- Compared to baseline (-4 weeks), PEG-to-PEG and ECU-to-PEG patients displayed clinically meaningful improvements (≥3-point increase⁴) in fatigue symptoms throughout the duration of the pegcetacoplan monotherapy (**Fig. 3**)
- At 28 weeks post-PEG dosing, the time adjusted data indicated that the mean FACIT-Fatigue scores for both treatment groups were close to the population norm⁵ (**Fig. 3**)
- At all time adjusted timepoints, there were no significant differences in the average FACIT-Fatigue scores for the ECU-to-PEG group compared to the PEG-to-PEG group (**Fig. 3**)

Figure 3. Post Hoc Time Adjusted FACIT-Fatigue Scores with Pegcetacoplan Treatment



ECU, eculizumab; FACIT, Functional Assessment of Chronic Illness Therapy; PEG, pegcetacoplan; SE, standard error

RESULTS, continued

Additional Clinical Outcomes and Hematologic Markers

- Over 70% of PEG-to-PEG and ECU-to-PEG patients were transfusion-free at Week 48 (**Table 2**)
- Patients in the PEG-to-PEG group showed a sustained decreased in ARC levels through Week 48 (**Table 2**; no significant difference between Week 16 and Week 48 in the PEG-to-PEG group; p=0.31^a)
- ECU-to-PEG patients demonstrated a significant decrease in ARC at Week 48 (**Table 2**; compared to Week 16, p<0.0001^a)
- PEG-to-PEG and ECU-to-PEG patients displayed decreased LDH levels following pegcetacoplan monotherapy (**Table 2**)
 - Post hoc time adjusted data for ARC and LDH also showed no significant differences at 28 Weeks post-PEG dosing (p=0.38^a and p=0.51^a, respectively).

^aUncorrected/nominal p-value

Table 2. Freedom From Transfusions, ARC, and LDH Endpoints

Outcome or Hematologic Marker	PEG-to-PEG			ECU-to-PEG		
	Baseline	Week 16	Week 48	Baseline	Week 16	Week 48
Freedom from Transfusions n (%)	N/A	35 (85.4)	30 (73.2) ^a	N/A	6 (15.4)	28 (71.8) ^a
ARC, ×10⁹ cells/L; NRR, 30-120×10⁹ cells/L Mean (SD)	217.5 (75.0)	77.1 (26.6)	80.0 (26.8)	216.2 (69.1)	221.8 (88.7)	94.0 (50.1)
LDH, U/L; NRR, 113-226 U/L Mean (SD)	257.5 (97.7)	189.1 (78.1)	222.7 (141.1)	308.6 (284.8)	353.2 (477.5)	224.1 (133.5)

^aFreedom from transfusions for pegcetacoplan monotherapy time period: PEG-to-PEG Day 1 to Week 48 (48 weeks total), ECU-to-PEG Week 16 to 48 (28 weeks total) ARC, absolute reticulocyte count; ECU-to-PEG, patients received eculizumab during the randomized controlled period and switched to pegcetacoplan during the open-label period after a 4-week run-in; LDH, lactate dehydrogenase; N/A, not applicable; NRR, normal reference range; PEG-to-PEG, patients received pegcetacoplan during the randomized controlled period and continued through Week 48 of the open-label period; PNH, paroxysmal nocturnal hemoglobinuria; SD, standard deviation

Treatment Emergent Adverse Events and Study Discontinuations

- While subjects were on PEG monotherapy, 24 subjects (30.0%) experienced at least 1 serious adverse event with 5 (6.3%) being deemed related to pegcetacoplan
- A total of 12 patients (15.0%) discontinued PEG prior to Week 48 due to a TEAE: 3 in RCP, 9 in OLP (7 ECU-to-PEG, 2 PEG-to-PEG) (**Table 3**)
- Common physician-reported adverse events for PEG patients were injection site reactions, hemolysis, and diarrhea (**Table 3**)

Table 3. TEAEs and Discontinuations

Patients With TEAEs, n (%)	PEG-to-PEG		ECU-to-PEG	
	Week 16 (n=41)	Week 48 (n=38)	Week 16 (n=39)	Week 48 (n=39)
Any TEAE	36 (87.8)	33 (86.8)	34 (87.2)	37 (94.9)
Mild	19 (46.3)	17 (44.7)	14 (35.9)	16 (41.0)
Moderate	9 (22.0)	8 (21.1)	15 (38.5)	12 (30.8)
Severe	8 (19.5)	8 (21.1)	5 (12.8)	9 (23.1)
Serious TEAEs	7 (17.1)	8 (21.1)	6 (15.4)	10 (25.6)
Discontinuations due to TEAEs	3 (7.3)	2 (5.3)	0	7 (17.9)
TEAEs of interest				
Infections and Infestations ^a	12 (29.3)	21 (55.3)	10 (25.6)	21 (53.8)
Hemolysis	4 (9.8)	7 (18.4)	9 (23.1)	8 (20.5)
Injection site reactions	15 (36.6)	7 (18.4)	1 (2.6)	13 (33.3)
Diarrhea	9 (22.0)	5 (13.2)	1 (2.6)	5 (12.8)

^aInfections and infestations defined as: upper respiratory tract infection, urinary tract infection, chronic sinusitis, diverticulitis, pyelonephritis acute, appendicitis, Bartholinitis, biliary sepsis, breast abscess, bronchitis, cystitis, device related sepsis, fungal skin infection, gastroenteritis, herpes virus infection, undefined infection, and malaria ECU-to-PEG, patients received eculizumab during the randomized controlled period and switched to pegcetacoplan during the open-label period after a 4-week run-in; PEG-to-PEG, patients received pegcetacoplan during the randomized controlled period and continued through Week 48 of the open-label period; TEAE, treatment-emergent adverse event

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All of the trial participants. **DISCLOSURES:** Peffault de Latour, R: reports conflicts with Novartis; consultancy, honoraria, research funding; Pfizer: consultancy, honoraria, research funding; Amgen: research funding; Alexion Pharmaceuticals Inc.: consultancy, honoraria, research funding; Szer, J: reports conflicts with Takeda; honoraria, speakers bureau; Pfizer: honoraria, speakers bureau; Novartis: consultancy, honoraria, research funding; Panse, J: reports conflicts with Blueprint Medicines; consultancy, honoraria, membership on an entity's Board of Directors or advisory committees; Alexion Pharmaceuticals Inc.: consultancy, honoraria, membership on an entity's Board of Directors or advisory committees; speakers bureau; Apellis: consultancy, honoraria, membership on an entity's Board of Directors or advisory committees; Chugai: speakers bureau; Pfizer: speakers bureau; Novartis: membership on an entity's Board of Directors or advisory committees; speakers bureau; F. 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