

CONCLUSIONS

- ✓ Clinically meaningful improvements in patient-reported fatigue were demonstrated among patients treated with pegcetacoplan, continuously through Week 48 in PEGASUS, and in those who switched from eculizumab to pegcetacoplan monotherapy
- ✓ Improved Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) scores in pegcetacoplan treated patients correlated with increased hemoglobin levels
- ✓ These results suggest that the FACIT-Fatigue scale is a valid patient-reported measure for assessing meaningful change in patients with paroxysmal nocturnal hemoglobinuria

INTRODUCTION

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and potentially life-threatening hematological disease characterized by hemolysis and thrombosis<sup>1</sup>
- C5-inhibitors (i.e., eculizumab [ECU] and ravulizumab) are commonly used to treat PNH, however, persistently low hemoglobin (Hb) levels in ECU patients impacts their quality of life
  - Historically, studies show that 80-96% of patients with PNH report persistent fatigue<sup>2,3</sup>, and 23% of patients report hospitalization due to their PNH-related symptoms<sup>3</sup>
- PEGASUS (NCT03500549) was a Phase 3, randomized, multi-center, open-label, active-comparator controlled study that evaluated the efficacy of pegcetacoplan treatment in patients with PNH and prior suboptimal response to ECU treatment
- Pecetacoplan (PEG), a C3-inhibitor recently approved by the US Food and Drug Administration, improved fatigue and was superior to ECU in improving hemoglobin levels at Week 16 of the PEGASUS study<sup>4</sup>

AIMS

These post hoc analyses compare patient-reported measures of fatigue to clinical PNH markers (i.e., Hb levels, absolute reticulocyte count [ARC], and indirect bilirubin levels) in PEG-treated patients with PNH through Week 48 of the PEGASUS study.

METHODS

Figure 1. PEGASUS Phase 3 Trial Design

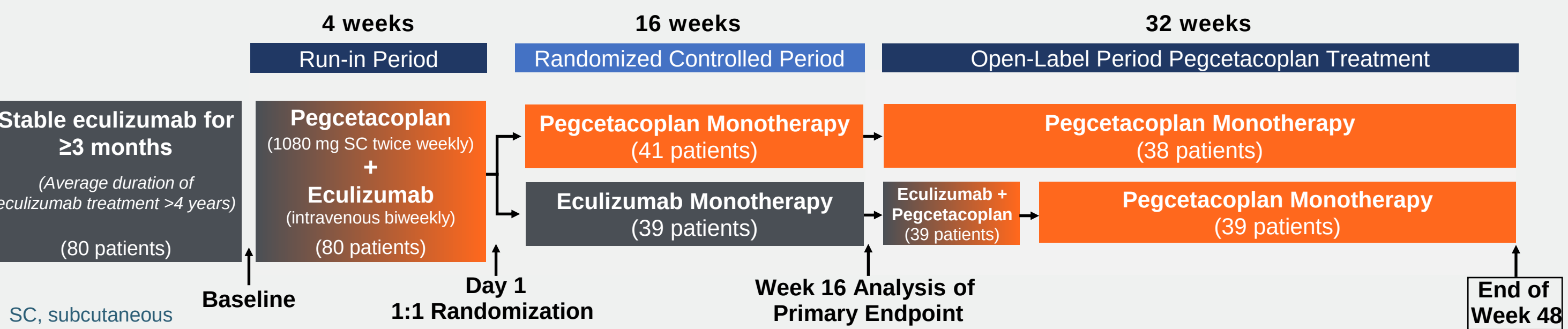


Table 1. Study Design

| Population                | Patients ≥18 years of age with PNH and Hb <10.5 g/dL despite stable treatment with ECU (≥ 3 months)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Week 48 Endpoints         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Efficacy Endpoints        | Change from baseline in Hb levels and FACIT-Fatigue scores                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Treatment Groups          | <ul style="list-style-type: none"><li>• <b>PEG-to-PEG:</b> Patients received PEG during the randomized controlled period and continued through Week 48 of the open-label period</li><li>• <b>ECU-to-PEG:</b> Patients received ECU during the randomized controlled period and switched to PEG during the open-label period after a 4-week run-in</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Measurements and Analysis | <ul style="list-style-type: none"><li>• Fatigue was assessed with the FACIT-Fatigue scale, version 4. Scores range from 0 to 52, higher scores are interpreted as lower levels of fatigue. Clinically meaningful improvements in fatigue are indicated by a ≥3-point score increase<sup>5</sup></li><li>• Spearman correlations assessed convergent validity. Responsiveness to change was evaluated by grouping patients according to increases in Hb (&lt;1 g/dL, ≥1 to &lt;2 g/dL, ≥2 g/dL), decreases in ARC (≥37.5x109 cells/L and &lt;37.5x109 cells/L) and indirect bilirubin (≥2.4 μmol/L and &lt;2.4 μmol/L). ARC and indirect bilirubin cut points were based on median split for each variable</li><li>• Mean changes by treatment from Week 17 to 48, including patients with transfusion events are described</li></ul> |

ARC, absolute reticulocyte count; ECU, eculizumab; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; PEG, pegcetacoplan; PNH, paroxysmal nocturnal hemoglobinuria

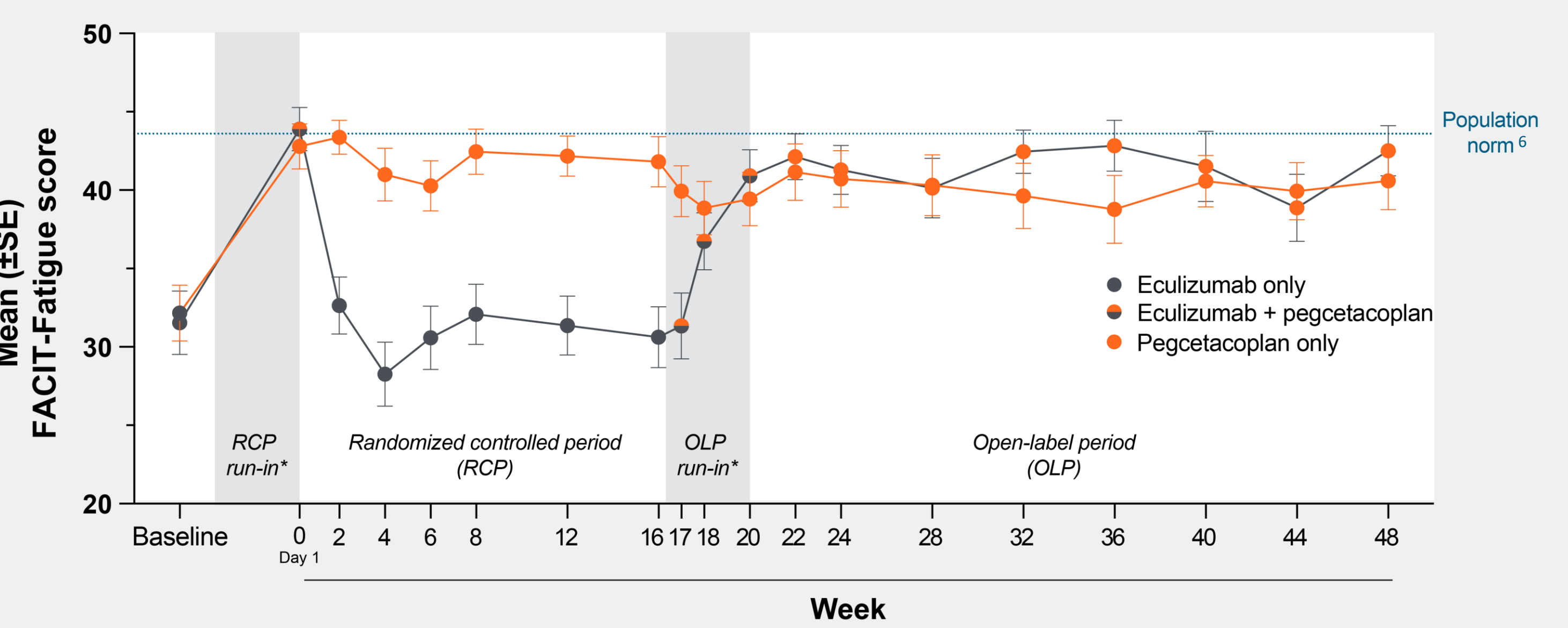
RESULTS

FACIT-Fatigue Scores Over Time and Correlations with Hemoglobin Levels

- PEG-to-PEG patients experienced sustained and clinically meaningful improvements in fatigue from Week 16 through Week 48 (**Fig. 2**; no significant difference in FACIT-Fatigue scores between Week 16 and Week 48 in the PEG-to-PEG group; p=0.82<sup>a</sup>)
- At Week 48, both PEG-to-PEG and ECU-to-PEG groups had similar FACIT-Fatigue scores (PEG-to-PEG: 40.6 and ECU-to-PEG: 42.5) (**Fig. 2**)
- At Week 48, FACIT-Fatigue scores were significantly correlated with Hb (r=0.31, p<0.05; **Table 2**)
- PEG-treated patients maintained the FACIT-Fatigue score and Hb level correlation through Week 48 (r=0.32, p<0.05; **Table 2**)

<sup>a</sup>Uncorrected/nominal p value

Figure 2. Mean FACIT-Fatigue Scores Over Time



<sup>a</sup>Pegcetacoplan run-in periods: 1) before randomization, for both PEG-to-PEG and ECU-to-PEG treatment groups; and 2) before the open-label period, for the ECU-to-PEG treatment group only. All observed/uncensored for transfusion data  
ECU, eculizumab; FACIT, Functional Assessment of Chronic Illness Therapy; OLP, open-label period; PEG, pegcetacoplan; RCP, randomized controlled period; SE, standard error

Table 2. FACIT-Fatigue Score Correlations<sup>a</sup> with Hemoglobin Levels

|                                | FACIT-Fatigue Score Day 1 | FACIT-Fatigue Score Week 16 | FACIT-Fatigue Score Week 48 |
|--------------------------------|---------------------------|-----------------------------|-----------------------------|
| Hemoglobin Levels <sup>b</sup> | 0.13                      | 0.48****                    | 0.32*                       |

<sup>a</sup> Spearman correlations; <sup>b</sup> Hemoglobin levels were assessed by lab and all patients with a FACIT-fatigue score and Hb level at Day 1, Week 16, and Week 48 were included in each time-point analysis.  
FACIT, Functional Assessment of Chronic Illness Therapy  
<sup>\*</sup>p<0.05, <sup>\*\*\*\*</sup>p<0.0001

Mean Changes in FACIT-Fatigue Scores by Changes in Hemoglobin Levels

- From Week 17 to Week 48, the group with the greatest improvement in Hb (≥2g/dL) showed a reduction in fatigue with a 13.2-point improvement in FACIT-Fatigue score (F=9.49, p<0.0001) (**Table 3**)
- No statistically different mean changes in FACIT-Fatigue scores were observed in the PEG-to-PEG Hb groups from Week 17 to Week 48, which shows treatment effects stayed consistent for most patients (**Table 3**)
- The patients in the ECU-to-PEG group showed an improvement in fatigue (F=4.52, p=0.01) with the largest reduction in the group, with an increase in Hb of ≥2g/dL (14.2-point improvement in FACIT-Fatigue scores) (**Table 3**)

RESULTS, continued

Table 3. Mean Change in FACIT-Fatigue Scores from Week 17 to 48 by Increases in Hemoglobin Levels

|                                | Increase in Hemoglobin level |                                |                         | Overall F (p value) |
|--------------------------------|------------------------------|--------------------------------|-------------------------|---------------------|
|                                | <1g/dL LS Mean (SE), N       | ≥1.0-<2.0 g/dL LS Mean (SE), N | ≥2 g/dL LS Mean (SE), N |                     |
| Overall FACIT-Fatigue Score    | 1.6 (1.60), 33               | -3.4 (4.96), 3                 | 13.2 (2.21), 19         | 9.49 (<0.0001)      |
| PEG-to-PEG FACIT-Fatigue Score | 1.4 (1.81), 20               | 0.7 (2.69), 9                  | 3.2 (8.24), 1           | 0.42 (0.7371)       |
| ECU-to-PEG FACIT-Fatigue Score | -5.6 (5.48), 3               | 4.2 (4.70), 4                  | 14.2 (2.20), 18         | 4.52 (0.0135)       |

ECU, eculizumab; 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; FACIT, Functional Assessment of Chronic Illness Therapy; LS, least-squares; PEG, pegcetacoplan; PEG-to-PEG, patients received pegcetacoplan during the randomized controlled period and continued through Week 48 of the open-label period; SE, standard error

Mean Changes in FACIT-Fatigue Scores by Decreases in Reticulocyte Count and Indirect Bilirubin

Patients with larger decreases in ARC and indirect bilirubin demonstrated clinically meaningful improvements in FACIT-Fatigue scores (**Table 4**).

Table 4. Mean Change in FACIT-Fatigue Scores from Week 17 to 48 by Decreases in Reticulocyte Count and Indirect Bilirubin

|                             | Decrease in Reticulocyte Count              |                                                          | Overall F (p value) | Decrease in Indirect Bilirubin        |                                       | Overall F (p value) |
|-----------------------------|---------------------------------------------|----------------------------------------------------------|---------------------|---------------------------------------|---------------------------------------|---------------------|
|                             | < Median (37.5x 109cells/L) LS Mean (SE), N | ≥ Median (37.55x10 <sup>9</sup> cells/L) LS Mean (SE), N |                     | < Median (2.4 μmol/L) LS Mean (SE), N | ≥ Median (2.4 μmol/L) LS Mean (SE), N |                     |
| Overall FACIT-Fatigue Score | 2.37 (1.90), 25                             | 8.32 (1.79), 28                                          | 5.20 (0.0268)       | 1.29 (2.01), 24                       | 8.70 (1.93), 26                       | 7.10 (0.0105)       |

FACIT, Functional Assessment of Chronic Illness Therapy; LS, least-squares; SE, standard error

Meaningful Changes in FACIT-Fatigue Scores

- PEG-to-PEG group showed a high percentage of responders early in treatment, by week 16, and remained high (less fatigue) from Week 16 to Week 48 (**Table 5**)
- In contrast, the ECU-to-PEG group showed a worsening of fatigue between baseline and Week 16, which then improved to the level of the PEG group after the patients were switched to PEG monotherapy from Week 17 to Week 48 (**Table 5**)

Table 5. Mean Changes and Percent Responders by Treatment Group for FACIT-Fatigue Score

|                                                  | Responder Threshold <sup>a</sup> |                     |                     |                     |
|--------------------------------------------------|----------------------------------|---------------------|---------------------|---------------------|
| Treatment Group                                  | Δ Score Mean (SD)                | ≥3 MCID % Responder | ≥4 MCID % Responder | ≥5 MCID % Responder |
| Baseline to Week 16 (including RIP) <sup>a</sup> |                                  |                     |                     |                     |
| PEG (n=36)                                       | 10.3 (11.03)                     | 30 (83.3%)          | 29 (80.6%)          | 26 (72.2%)          |
| ECU (n=35)                                       | -1.2 (8.75)                      | 10 (28.6%)          | 9 (25.7%)           | 8 (22.9%)           |
| Week 16 to Week 48                               |                                  |                     |                     |                     |
| PEG-to-PEG (n=28)                                | -0.5 (7.38)                      | 8 (28.6%)           | 6 (21.4%)           | 4 (14.3%)           |
| ECU-to-PEG (n=28)                                | 10.9 (10.86)                     | 23 (82.1%)          | 22 (78.6%)          | 21.75.0%)           |

<sup>a</sup>Increase of ≥3 points on the FACIT-Fatigue scale is considered clinically meaningful<sup>5</sup>

<sup>a</sup>Analysis performed on all available data regardless of intercurrent events  
ECU, eculizumab; 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; FACIT, Functional Assessment of Chronic Illness Therapy; MCID: Minimal Clinically Important Difference; PEG, pegcetacoplan; PEG-to-PEG, patients received pegcetacoplan during the randomized controlled period and continued through Week 48 of the open-label period; SD, standard deviation; RIP, run-in period, where patients received both eculizumab and pegcetacoplan

