ORIGINAL ARTICLE

# Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Peter Hillmen, M.B., Ch.B., Ph.D., Jeff Szer, M.B., B.S., Ilene Weitz, M.D., Alexander Röth, M.D., Britta Höchsmann, M.D., Jens Panse, M.D., Kensuke Usuki, M.D., Ph.D., Morag Griffin, B.M.Sc., M.B., Ch.B., Jean-Jacques Kiladjian, M.D., Ph.D., Carlos de Castro, M.D., Hisakazu Nishimori, M.D., Ph.D., Lisa Tan, R.N., Mohamed Hamdani, M.S., Pascal Deschatelets, Ph.D., Cedric Francois, M.D., Ph.D., Federico Grossi, M.D., Ph.D., Temitayo Ajayi, M.D., Antonio Risitano, M.D., Ph.D., and Régis Peffault de la Tour, M.D., Ph.D.

## ABSTRACT

### BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired disease characterized by chronic complement-mediated hemolysis. C5 inhibition controls intravascular hemolysis in untreated PNH but cannot address extravascular hemolysis. Pegcetacoplan, a pegylated peptide targeting proximal complement protein C3, potentially inhibits both intravascular and extravascular hemolysis.

### METHODS

We conducted a phase 3 open-label, controlled trial to assess the efficacy and safety of pegcetacoplan as compared with eculizumab in adults with PNH and hemoglobin levels lower than 10.5 g per deciliter despite eculizumab therapy. After a 4-week run-in phase in which all patients received pegcetacoplan plus eculizumab, we randomly assigned patients to subcutaneous pegcetacoplan monotherapy (41 patients) or intravenous eculizumab (39 patients). The primary end point was the mean change in hemoglobin level from baseline to week 16. Additional clinical and hematologic markers of hemolysis and safety were assessed.

### RESULTS

Pegcetacoplan was superior to eculizumab with respect to the change in hemoglobin level from baseline to week 16, with an adjusted (least squares) mean difference of 3.84 g per deciliter ($P<0.001$). A total of 35 patients (85%) receiving pegcetacoplan as compared with 6 patients (15%) receiving eculizumab no longer required transfusions. Noninferiority of pegcetacoplan to eculizumab was shown for the change in absolute reticulocyte count but not for the change in lactate dehydrogenase level. Functional Assessment of Chronic Illness Therapy–Fatigue scores improved from baseline in the pegcetacoplan group. The most common adverse events that occurred during treatment in the pegcetacoplan and eculizumab groups 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%). There were no cases of meningitis in either group.

### CONCLUSIONS

Pegcetacoplan was superior to eculizumab in improving hemoglobin and clinical and hematologic outcomes in patients with PNH by providing broad hemolysis control, including control of intravascular and extravascular hemolysis. (Funded by Apellis Pharmaceuticals; PEGASUS ClinicalTrials.gov, NCT03500549.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Hillmen at Bexley Wing, St. James's University Hospital, Beckett St., Leeds, LS9 7TF United Kingdom, or at p.hillmen@leeds.ac.uk.

N Engl J Med 2021;384:1028-37.
DOI: 10.1056/NEJMoa2029073

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, clonal, nonmalignant hematologic disease characterized by complement-mediated hemolysis (with or without hemoglobinuria), fatigue, increased susceptibility to thrombosis, and some degree of bone marrow dysfunction.[1] PNH results from the expansion of abnormal hematopoietic clones that lack cell-surface complement inhibitory proteins attached to the membrane through glycosylphosphatidylinositol anchors.[2-5] At least two of the missing glycosylphosphatidylinositol-linked proteins, CD55 and CD59, are key regulators of the complement pathway and protect host cells from complement-mediated removal.[6-8] This complement dysregulation leads to chronic hemolysis and thrombosis characteristic of PNH.[1,9] Manifestations of hemolysis are due directly to the increased sensitivity of PNH cells to complement.[5,10]

Intravascular hemolysis of CD59-deficient erythrocytes results in the hemoglobinuria after which PNH is named.[6,11] The development of targeted terminal complement C5 inhibitors has transformed outcomes for patients with PNH by controlling intravascular hemolysis. In addition, C5 inhibitors prevent terminal complement-mediated platelet and white-cell activation and destruction, thereby leading to a marked reduction in thrombosis, which is the main life-threatening complication of PNH.[12,13] C5 inhibition also ameliorates anemia and reduces the need for transfusions and prevents many PNH complications such as kidney failure and pulmonary hypertension.[12,14,15]

PNH erythrocytes also lack CD55, leading to reduction in C3-convertase enzyme dissociation, increase in the production of C3 fragments, and subsequent opsonization.[7] Although eculizumab is effective in preventing C5-dependent intravascular hemolysis mediated by the membrane-attack complex, surviving PNH erythrocytes become opsonized with C3 fragments and are removed by extravascular hemolysis in the liver and spleen.[16] Extravascular hemolysis is observed in most patients with PNH who are being treated with C5 inhibitors and leads to reduced erythrocyte half-life (10 to 13 days).[16,17] Extravascular hemolysis can manifest as persistent anemia despite C5 inhibitor treatment and may contribute to the need for continued blood transfusions.[16-19]

Pegcetacoplan is a pegylated pentadecapeptide that targets complement C3[20] to control both intravascular and extravascular hemolysis. The PEGASUS trial is a 48-week, phase 3, randomized, multicenter, open-label, active-comparator–controlled trial of the efficacy and safety of pegcetacoplan as compared with eculizumab in patients with PNH and a hemoglobin level of less than 10.5 g per deciliter despite treatment with eculizumab. We report here the primary efficacy and safety outcomes from the 16-week randomized, controlled period.

*A Quick Take is available at NEJM.org*

## METHODS

### PATIENTS

Adult patients (≥18 years of age) in whom PNH was diagnosed by high-sensitivity flow cytometry and who had hemoglobin levels of less than 10.5 g per deciliter while they were receiving stable doses of eculizumab for at least 3 months before screening were eligible for participation in the trial. Additional information about eligibility criteria, end points, and statistical analyses is provided in the Methods section of the Supplementary Appendix, available with the full text of this article at NEJM.org. All patients provided written informed consent before enrollment.

### TRIAL DESIGN

The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and the protocol (available at NEJM.org) was approved by the relevant institutional review board or ethics committee at each site. The trial was designed by the sponsor (Apellis Pharmaceuticals) and the academic authors. The sponsor conducted trial oversight and provided the pegcetacoplan; eculizumab was provided to sites where it was not part of the standard of care. Trial investigators collected the data, which were analyzed by the sponsor. The first author and senior industry author wrote the first draft of the manuscript; medical writing assistance was paid for by the sponsor. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The sponsor reviewed and provided feedback on the manuscript. Full editorial control of the manuscript was maintained by the authors, all of whom provided their final approval of the manuscript submitted for publication. Confidentiality agreements were in place between all the authors and the sponsor.

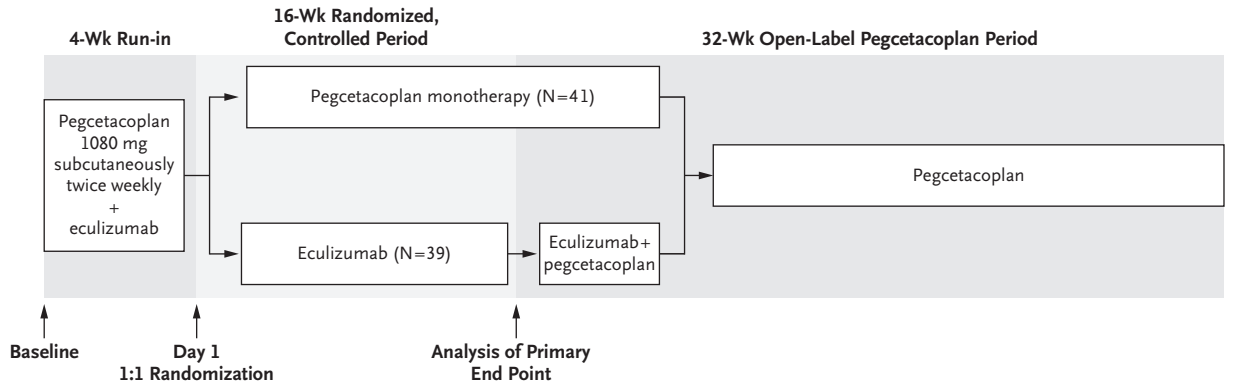



**Figure 1. Trial Design.**

The trial treatment period consisted of three parts: a 4-week run-in period, followed by a 16-week randomized, controlled period during which patients received either pegcetacoplan or eculizumab as monotherapy, and a 32-week open-label period during which patients received pegcetacoplan. Patients who received eculizumab during the 16-week randomized, controlled period continued to receive eculizumab in addition to pegcetacoplan for the first 4 weeks of the open-label period.

The trial treatment period consisted of three parts (Fig. 1). During a 4-week run-in phase, all the patients continued to receive their current dose of eculizumab with the addition of twice-weekly pegcetacoplan (1080 mg), which the patients administered themselves subcutaneously. After the run-in phase, patients were randomly assigned, in a 1:1 ratio, to monotherapy with pegcetacoplan or eculizumab for 16 weeks (randomized, controlled period). This period was followed by a 32-week period in which all patients received open-label pegcetacoplan. Randomization was stratified according to the number of packed red-cell transfusions patients had received during the 12 months before screening (<4 or ≥4) and the platelet count at screening (<100,000 or ≥100,000 cells $\times 10^9$ per liter).

### CLINICAL EFFICACY

The primary end point was the change in hemoglobin level from baseline to week 16 during the randomized, controlled period. Key secondary end points were the proportion of patients who did not require a transfusion during the randomized, controlled period and the change from baseline to week 16 in absolute reticulocyte count, lactate dehydrogenase (LDH) level, and score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale (scores range from 0 to 52, with higher scores indicating less fatigue). Additional end points are described in the Supplementary Appendix.

### SAFETY

Safety end points included the incidence and severity of adverse events that occurred during the run-in phase or beyond, the incidence of thromboembolic events, and the changes from baseline in laboratory and electrocardiographic variables.

### STATISTICAL ANALYSIS

The between-group comparison for the primary end point was performed with the use of a mixed-effect model for repeated measures (MMRM), with baseline hemoglobin as a continuous variable, time point as a categorical variable, and treatment group, stratification variables, and time-by-treatment interaction as fixed effects. Transfusions were considered to be intercurrent events that could confound the results, and data after the first transfusion were censored. To control for a type 1 error, the key secondary end points were tested for noninferiority in the following hierarchical manner if superiority was declared for the primary end point: the proportion of patients who did not require a transfusion during the randomized, controlled period, followed by change from baseline to week 16 in absolute reticulocyte count, LDH level, and FACIT–F score. Analyses were also conducted with all observed data considered (with no censoring of post-transfusion data). Additional details are shown in the Methods section of the Supplementary Appendix.

## RESULTS

### PATIENTS

Of 102 patients screened, 80 (49 women and 31 men) met the entry criteria and were enrolled across 44 centers; 41 patients were randomly assigned to receive pegcetacoplan and 39 to receive eculizumab during the 16-week randomized, controlled period (Fig. S1 in the Supplementary Appendix). All 39 patients assigned to receive eculizumab completed the 16 weeks of therapy; 3 of the 41 patients in the pegcetacoplan group discontinued therapy before week 16 owing to breakthrough hemolysis. The trial was conducted from June 2018 through November 2019.

Demographic and baseline characteristics were generally balanced between the two groups (Table 1). The mean time from diagnosis of PNH to the first day of the 4-week run-in phase was 10.18 years overall and was longer in the eculizumab group than in the pegcetacoplan group (11.68 years vs. 8.74 years), although this difference was not statistically significant. The duration of previous eculizumab treatment was similar in the two groups. In the overall trial population, 25 patients (31%) had a history of thrombosis and 20 (25%) had a history of aplastic anemia. Twenty-four patients (30%) were receiving eculizumab doses higher than 900 mg every 2 weeks. Additional details are provided in the Supplementary Appendix.

### CLINICAL EFFICACY

#### *Primary End Point*

Pegcetacoplan was superior to eculizumab with respect to the change in hemoglobin level from baseline to week 16 (Fig. 2). The adjusted (least squares) mean change from baseline was 2.37 g per deciliter with pegcetacoplan and –1.47 g per deciliter with eculizumab, for a mean difference between treatments of 3.84 g per deciliter (95% confidence interval [CI], 2.33 to 5.34; P<0.001) at week 16 (Fig. 2B). The results of a supportive analysis of the primary end point that included all available data (not censored for transfusions) were consistent with the results of the primary analysis; the adjusted mean change from baseline to week 16 with inclusion of all available data was 2.66 g per deciliter with pegcetacoplan and −0.03 g per deciliter with eculizumab, for a mean difference between treatments of 2.69 g per deciliter (95% CI, 1.99 to 3.38; P<0.001).

Increased hemoglobin levels in patients receiving pegcetacoplan monotherapy, as compared with patients receiving eculizumab monotherapy, were seen as early as week 2 of the 16-week randomized, controlled period and were maintained throughout the 16-week period (Fig. 2A). In a subgroup analysis according to pretrial transfusion requirements, improvements from baseline in hemoglobin level in the pegcetacoplan group (2.97 g per deciliter among patients with <4 transfusions in the 12 months before screening and 2.11 g per deciliter among patients with ≥4 transfusions) were consistent with the improvements in the overall cohort; however, in the eculizumab group, patients with fewer than 4 transfusions in the 12 months before screening had a decrease in hemoglobin of 0.01 g per deciliter, and patients with 4 or more transfusions in the 12 months before screening had a decrease in hemoglobin of 4.02 g per deciliter (Fig. 2B). When all observed data were considered, the results of all primary and key secondary analyses were consistent with the MMRM analyses in which post-transfusion data were censored.

#### *Key Secondary End Points*

Over the 16-week randomized, controlled period, 35 patients (85%) in the pegcetacoplan group were transfusion-free, whereas only 6 (15%) in the eculizumab group were transfusion-free (P<0.001) (Fig. 3). Consistent effects regarding freedom from transfusion were seen regardless of the transfusion stratum in the 12 months before trial initiation (Table S1).

The absolute reticulocyte count decreased with pegcetacoplan and slightly increased with eculizumab (adjusted mean [±SE] changes, $-136\pm7\times10^9$ per liter and $28\pm12\times10^9$ per liter, respectively), a finding that showed the noninferiority of pegcetacoplan to eculizumab (Fig. 3 and Fig. S2A). Noninferiority was not shown for the change from baseline in LDH level (Fig. 3); the adjusted mean change from baseline was –15±43 U per liter in the pegcetacoplan group and –10±71 U per liter in the eculizumab group. Additional information is provided in the Supplementary Appendix.

FACIT–F scores increased with pegcetacoplan by 9.2 points and decreased with eculizumab by 2.7 points (Fig. S2C), resulting in an adjusted mean difference of 11.9 points (95% CI, 5.49 to

**Table 1. Demographic and Clinical Characteristics of Patients at Baseline.***

| Characteristic | Pegcetacoplan (N=41) | Eculizumab (N=39) |
|---|---|---|
| Age | | |
| Mean (range) — yr | 50.2 (19–81) | 47.3 (23–78) |
| >65 yr — no. (%) | 10 (24) | 7 (18) |
| Female sex — no. (%) | 27 (66) | 22 (56) |
| Race — no. (%)† | | |
| Asian | 5 (12) | 7 (18) |
| Black | 2 (5) | 0 |
| White | 24 (59) | 25 (64) |
| Other | 0 | 1 (3) |
| Not reported | 10 (24) | 6 (15) |
| Body-mass index‡ | 26.7±4.3 | 25.9±4.3 |
| No transfusions within previous 12 mo — no. (%) | 10 (24) | 10 (26) |
| History of aplastic anemia — no. (%) | 11 (27) | 9 (23) |
| Median time since PNH diagnosis (range) — yr | 6.0 (1–31) | 9.7 (1–38) |
| Median duration of prior treatment with eculizumab (range) — yr | 4.4 (0.4–17.1) | 3.4 (0.3–13.8) |
| Eculizumab dose at screening — no. (%) | | |
| 900 mg every 2 wk | 26 (63) | 30 (77) |
| 1200 mg every 2 wk§ | 13 (32) | 9 (23) |
| 1500 mg every 2 wk | 2 (5) | 0 |
| Platelets — $\times 10^{-9}$/liter | 166.6±98.3 | 146.9±68.8 |
| ≥4 transfusions in previous 12 mo — no. (%) | 21 (51) | 23 (59) |
| Hemoglobin — g/dl¶ | 8.69±1.08 | 8.68±0.89 |
| Reticulocyte count — $\times 10^{-9}$/liter (normal reference range) | 217.5±75.0 (30–120) | 216.2±69.1 (30–120) |
| Lactate dehydrogenase — U/liter (normal reference range) | 257.5±97.6 (113–226) | 308.6±284.8 (113–226) |
| Total bilirubin — μmol/liter (normal reference range) | 42.5±31.5 (1.7–18.8) | 40.5±26.6 (1.7–18.8) |
| Indirect bilirubin — μmol/liter | 34.7±28.5 | 32.9±23.0 |
| FACIT–F score‖ | 32.2±11.4 | 31.6±12.5 |

* Plus–minus values are means ±SD. PNH denotes paroxysmal nocturnal hemoglobinuria.
† Race and ethnic group were reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ One patient in the pegcetacoplan group received 900 mg of eculizumab every 11 days.
¶ The normal reference range for women is 12 to 16 and for men is 13.6 to 18.
‖ Scores on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT–F) scale range from 0 to 52, with higher scores indicating less fatigue.

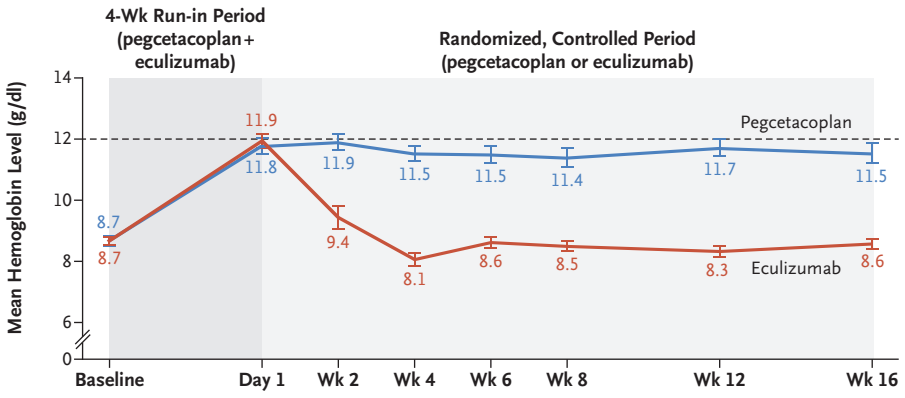
18.25) at week 16 (Fig. 3). This difference was considered to be clinically significant, but noninferiority was not assessed because of the prespecified statistical hierarchical testing rules. Furthermore, 73% of patients in the pegcetacoplan group had at least a 3-point increase in FACIT–F scores at week 16, as compared with 0% in the eculizumab group; a 3-point change is considered clinically significant.

A greater percentage of patients in the pegcetacoplan group than in the eculizumab group had normalization of key hematologic variables — hemoglobin level (34% vs. 0%), reticulocyte count (78% vs. 3%), LDH level (71% vs. 15%), and total bilirubin level (63% vs. 8%). (Additional information on FACIT–F scores and hematologic variables is available in Table S2.)

### SAFETY

Adverse events that occurred during treatment were recorded in 36 patients (88%) receiving pegcetacoplan and in 34 (87%) receiving ecu-

A




| No. with Available Data | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pegcetacoplan | 41 | 40 | 40 | 40 | 39 | 37 | 38 | 37 |
| Eculizumab | 39 | 37 | 38 | 39 | 36 | 39 | 39 | 38 |

B

| Subgroup | No. of Patients | | Adjusted Change in LS Mean Hemoglobin | | Difference (95% CI) |
|---|---|---|---|---|---|
| | Pegcetacoplan | Eculizumab | Pegcetacoplan | Eculizumab | |
| | | | *g/dl±SE* | | |
| Censored for transfusion events, all values after intercurrent events set to missing | 41 | 39 | 2.37±0.36 | −1.47±0.67 | 3.84 (2.33–5.34) |
| All available data, regardless of tranfusion events | 41 | 39 | 2.66±0.25 | −0.03±0.26 | 2.69 (1.99–3.38) |
| No. of transfusions in previous 12 mo | | | | | |
| <4 | 20 | 16 | 2.97±0.36 | −0.01±0.49 | 2.98 (1.73–4.23) |
| ≥4 | 21 | 23 | 2.11±0.60 | −4.02±2.40 | 6.13 (0.79–11.48) |

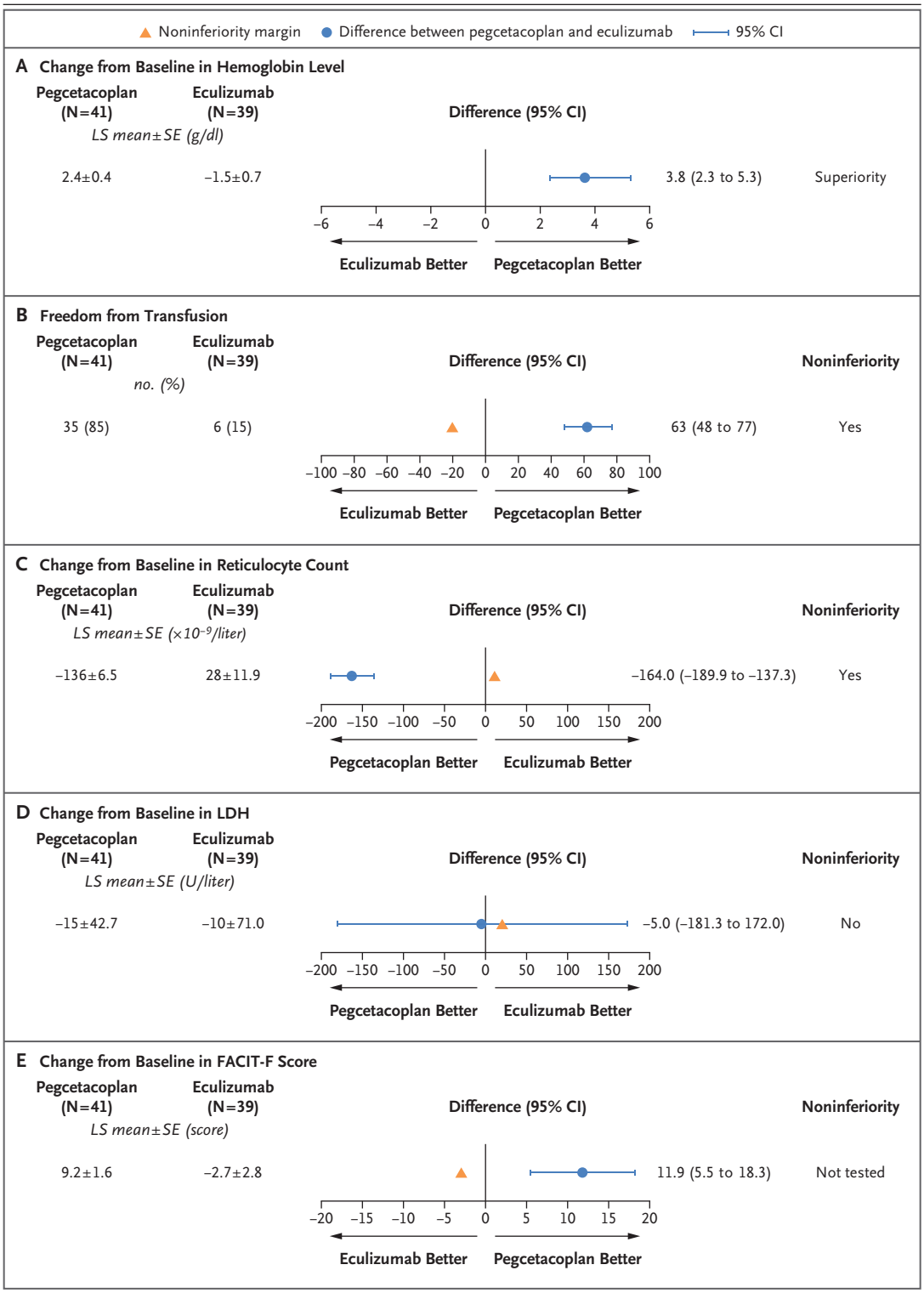
**Figure 2. Hemoglobin Levels from Baseline to Week 16.**

Panel A shows adjusted mean hemoglobin levels from baseline to week 16 and includes all the available data for all patients, regardless of transfusion events. Week 8 data include three patients in the pegcetacoplan group who had discontinued the trial and one patient with missing data. The dashed line indicates the lower limit of the normal range for female patients. I bars indicate standard errors. Panel B shows the primary end point, the adjusted change in least-squares (LS) mean (±SE) hemoglobin level from baseline to week 16, for the total patient population (both with data censored and data not censored for transfusion events) and according to transfusion history.

lizumab (Table 2). The most common adverse events in the pegcetacoplan and eculizumab groups 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%). The majority of injection-site reactions were mild and occurred early in the trial; none resulted in discontinuation. Diarrhea events were mostly mild single episodes. The incidence of serious adverse events was also similar in the two groups, with events reported in 7 patients (17%) receiving pegcetacoplan and in 6 (15%) receiving eculizumab (Table 2).

Infections were reported in 12 patients (29%) in the pegcetacoplan group and in 10 (26%) in the eculizumab group (Table 2). Meningitis was not reported in either treatment group. One case of sepsis was reported during the run-in period and was considered by the principal investigator to be unrelated to the initiation of pegcetacoplan treatment. No patient had a thrombotic event, and no deaths occurred during the trial.

Breakthrough hemolysis was reported in 4 patients (10%) receiving pegcetacoplan and in 9 (23%) receiving eculizumab. All four pegcetacoplan-treated patients who had breakthrough hemolysis had an elevation of LDH level to more than 3 times the upper limit of the normal range. The breakthrough hemolysis was associated with a rapid increase in LDH level indicating intravascular hemolysis, occurred without identifiable triggers or detectable anti-pegceta-




coplan antibodies, and resulted in three patients discontinuing treatment with pegcetacoplan and switching back to treatment with eculizumab. One patient had a hemolysis event with a maximum severity of "severe" on trial days 47 through 53, one patient had a moderate hemolysis event on trial days 49 through 56, and one patient had a moderate hemolysis event on trial days 36

**Figure 3 (facing page). Changes in Primary and Key Secondary Efficacy End Points from Baseline to Week 16.**

Shown are data on the primary (Panel A) and key secondary (Panels B through E) efficacy end points. Adjusted least-squares (LS) means (±SE) were calculated with the use of mixed-model repeated measures analysis. The differences are adjusted for stratification variables. Key secondary end-point analyses were based on prespecified noninferiority margins. Noninferiority was achieved if the lower or upper limit of the 95% confidence interval of the treatment difference met the prespecified margin. Key secondary end points were tested in a hierarchical manner for noninferiority if superiority was declared for the primary end point. Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F; scores range from 0 to 52, with higher scores indicating less fatigue) were not tested for noninferiority because the between-group difference in lactate dehydrogenase (LDH) level did not meet the noninferiority criterion. No further end points were tested. CI denotes confidence interval.

through 39. All 39 patients in the eculizumab group crossed over to the open-label pegcetacoplan monotherapy group for a 4-week run-in period during which they received eculizumab and pegcetacoplan, followed by 28 weeks of monotherapy (full patient data are provided in the Supplementary Appendix and Table S4).

## DISCUSSION

The primary finding of this trial is that pegcetacoplan treatment, which targets C3, was associated with a significantly greater increase in hemoglobin level than that observed in patients treated with the C5 inhibitor eculizumab. Despite treatment with eculizumab for an average of 5 years, with 30% receiving doses that were higher than the doses approved for PNH, the trial population remained severely anemic (mean baseline hemoglobin level, 8.7 g per deciliter), continued to be transfusion-dependent (with 75% requiring at least one transfusion during the previous year), and reported considerable fatigue, with a mean baseline FACIT–F score of 32 (with a score of 43.6 considered normal for a healthy adult).[21] In addition to the increase in hemoglobin level, more than one third of the patients treated with pegcetacoplan showed normalized levels of hemoglobin at week 16 and most (85%) did so without receiving a transfusion, whereas only 15% in the eculizumab group were transfusion-free during the 16-week randomized period. Furthermore, the effect on freedom

**Table 2. Adverse Events That Occurred during the 16-Week Randomized, Controlled Period.**

| Event | Pegcetacoplan (N=41) | Eculizumab (N=39) |
|---|---|---|
| | *no. of patients (%)* | |
| Any adverse event occurring during treatment | 36 (88) | 34 (87) |
| Adverse event in >5% of patients in either group | | |
| Injection-site erythema | 7 (17) | 0 |
| Injection-site reaction | 5 (12) | 0 |
| Injection-site swelling | 4 (10) | 0 |
| Asthenia | 3 (7) | 3 (8) |
| Injection-site induration | 3 (7) | 0 |
| Fatigue | 2 (5) | 6 (15) |
| Pyrexia | 2 (5) | 2 (5) |
| Vaccination-site pain from any vaccine* | 0 | 2 (5) |
| Back pain | 3 (7) | 4 (10) |
| Pain in arms or legs | 3 (7) | 1 (3) |
| Diarrhea | 9 (22) | 1 (3) |
| Abdominal pain | 5 (12) | 4 (10) |
| Nausea | 2 (5) | 2 (5) |
| Vomiting | 0 | 3 (8) |
| Viral upper respiratory tract infection | 2 (5) | 2 (5) |
| Hemolysis | 4 (10) | 9 (23) |
| Anemia | 0 | 5 (13) |
| Headache | 3 (7) | 9 (23) |
| Dizziness | 1 (2) | 4 (10) |
| Hypertension | 3 (7) | 1 (3) |
| Dyspnea | 1 (2) | 2 (5) |
| Oropharyngeal pain | 0 | 2 (5) |
| Hyperbilirubinemia | 0 | 2 (5) |
| Anxiety | 1 (2) | 2 (5) |
| Insomnia | 0 | 2 (5) |
| Palpitations | 0 | 2 (5) |
| Chromaturia | 0 | 2 (5) |
| Serious adverse events occurring during treatment | | |
| Any | 7 (17) | 6 (15) |
| Occurring in >1 patient in the pegcetacoplan group | | |
| Hemolysis | 2 (5) | 1 (3) |

* Patients were required to receive vaccinations against *Neisseria meningitides* types A, C, W, Y, and B, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B within 2 years before receiving the first dose of pegcetacoplan or within 14 days after the first dose.

from transfusion was consistent regardless of the transfusion burden during the previous year.

Markers of extravascular hemolysis such as reticulocytosis and hyperbilirubinemia were normalized in most patients in the pegcetacoplan group at week 16. Markers of intravascular hemolysis, notably LDH level, were relatively well controlled at baseline, as expected with treatment with a C5 complement inhibitor, and remained well controlled at week 16 in both treatment groups. These results show that inhibition of complement C3 was adequate to maintain control of intravascular hemolysis and also prevent extravascular hemolysis. Our data show that 71% of patients receiving pegcetacoplan had normalization of LDH levels at week 16, as compared with 15% of patients receiving eculizumab. Of note, reduction of mean LDH level to within the normal range was seen by the end of the run-in period and was maintained in patients receiving pegcetacoplan throughout the randomized, controlled period.

The effect of improvements in hemoglobin levels and control of underlying hemolysis translates not only to clinical variables such as freedom from transfusion but also to improvements in patient-reported outcomes. Fatigue is the most commonly reported symptom in patients with PNH and can have a tremendous adverse effect on quality of life.[22] Patients receiving pegcetacoplan had an improvement of 11.9 points on the FACIT–F scale (an increase of >3 points is generally considered clinically meaningful in other disease states). These improvements and differences between pegcetacoplan and eculizumab were evident irrespective of whether data after transfusions were included in analyses (Fig. S2); however, the open-label trial design does not exclude the potential for bias, and these improvements must be interpreted carefully.

A potential concern with broad complement inhibition is the possibility of increased risk of encapsulated bacterial infections.[23,24] The inhibition of the terminal complement leads to a well-defined risk of neisseria infection.[25] In the PEGASUS trial, no cases of meningococcal infection were noted in either group, and no difference in the incidence of infections was discerned between the two groups, with 29% and 26% of patients in the pegcetacoplan and eculizumab groups, respectively, reporting infections. Although these findings are encouraging, longer-term data on the incidence of infection with proximal complement inhibition are needed. Overall, safety and the side-effect profile were similar in the pegcetacoplan and eculizumab groups. As expected with the introduction of patients to frequent subcutaneous infusions that they administered themselves, injection-site reactions were the most common adverse events reported by patients in the pegcetacoplan group, but most events were mild, occurred early in the trial, and did not lead to any discontinuations.

Breakthrough hemolysis was reported more often in patients who received eculizumab than in those who received pegcetacoplan; however, three patients discontinued treatment with pegcetacoplan owing to a recurrence of intravascular hemolysis. Pharmacokinetic factors or underlying disease severity (details provided in the Supplementary Appendix) may have played a role and suggest that a small subgroup of patients may require dose adjustments of pegcetacoplan after cessation of eculizumab; this warrants further study. Lack of adherence to the trial drug was not observed in the three patients who discontinued pegcetacoplan.

Clinical data from the three patients who discontinued the trial were not collected after the time these patients stopped treatment with pegcetacoplan, and this may have had some effect on the differences observed between the treatment groups after the point of discontinuation. However, the extent of the effect would be difficult to assess, and data from these three patients before they stopped treatment with pegcetacoplan are included in the primary MMRM analysis.

The PEGASUS trial showed that in patients with persistent anemia despite eculizumab therapy, the C3 inhibitor pegcetacoplan was superior to the C5 inhibitor eculizumab with respect to the change from baseline to week 16 in hemoglobin level and provided improvements in key hematologic and clinical variables, such as freedom from transfusion. Adverse effects included mainly injection-site irritation and mild diarrhea. In this population, treating intravascular hemolysis as well as preventing extravascular hemolysis by proximal complement inhibition with pegcetacoplan may result in better control of disease than treatment with eculizumab.

Supported by Apellis Pharmaceuticals.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

## APPENDIX

The authors' affiliations are as follows: the Department of Haematology, St. James's University Hospital, Leeds (P.H., M.G.), and Lisa Tan Pharma Consulting, Cambridge (L.T.) — both in the United Kingdom; the Department of Clinical Haematology, Peter MacCallum Cancer Center and Royal Melbourne Hospital, Melbourne, VIC, Australia (J.S.); Jane Anne Nohl Division of Hematology, Keck School of Medicine of USC, Los Angeles (I.W.); the Department of Hematology, West German Cancer Center University Hospital Essen, University of Duisburg-Essen, Essen (A. Röth), the Institute of Transfusion Medicine, University of Ulm and Institute of Clinical Transfusion Medicine and Immunogenetics, German Red Cross Blood Transfusion Service and University Hospital Ulm, Ulm (B.H.), and the Department of Oncology, Hematology, Hemostaseology and Stem Cell Transplantation, University Hospital RWTH Aachen, Aachen (J.P.) — all in Germany; the Department of Hematology, NTT Medical Center Tokyo, Tokyo (K.U.), and the Department of Hematology and Oncology, Okayama University Hospital, Okayama (H.N.) — both in Japan; Centre d'Investigations Cliniques (J.-J.K.) and the French Reference Center for Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria (R.P.T.), Hôpital Saint-Louis, Assistance Publique–Hôpitaux de Paris, Université de Paris, Paris; the Department of Medicine, Division of Hematologic Malignancies and Cellular Therapy, Duke University, Durham, NC (C.C.); Apellis Pharmaceuticals, Waltham, MA (M.H., P.D., C.F., F.G., T.A.); and the Hematology and BMT Unit, AORN San Giuseppe Moscati, Avellino, Italy (A. Risitano).

## REFERENCES

**1.** Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. Nat Rev Dis Primers 2017;3:17028.

**2.** Bessler M, Mason PJ, Hillmen P, et al. Paroxysmal nocturnal haemoglobinuria (PNH) is caused by somatic mutations in the PIG-A gene. EMBO J 1994;13:110-7.

**3.** Takeda J, Miyata T, Kawagoe K, et al. Deficiency of the GPI anchor caused by a somatic mutation of the PIG-A gene in paroxysmal nocturnal hemoglobinuria. Cell 1993;73:703-11.

**4.** Hillmen P, Bessler M, Mason PJ, Watkins WM, Luzzatto L. Specific defect in N-acetylglucosamine incorporation in the biosynthesis of the glycosylphosphatidylinositol anchor in cloned cell lines from patients with paroxysmal nocturnal hemoglobinuria. Proc Natl Acad Sci U S A 1993;90:5272-6.

**5.** Yamashina M, Ueda E, Kinoshita T, et al. Inherited complete deficiency of 20-kilodalton homologous restriction factor (CD59) as a cause of paroxysmal nocturnal hemoglobinuria. N Engl J Med 1990;323:1184-9.

**6.** Boccuni P, Del Vecchio L, Di Noto R, Rotoli B. Glycosyl phosphatidylinositol (GPI)-anchored molecules and the pathogenesis of paroxysmal nocturnal hemoglobinuria. Crit Rev Oncol Hematol 2000;33:25-43.

**7.** Kinoshita T, Medof ME, Nussenzweig V. Endogenous association of decay-accelerating factor (DAF) with C4b and C3b on cell membranes. J Immunol 1986;136:3390-5.

**8.** Ninomiya H, Sims PJ. The human complement regulatory protein CD59 binds to the alpha-chain of C8 and to the "b" domain of C9. J Biol Chem 1992;267:13675-80.

**9.** Tumen J, Kline LB, Fay JW, et al. Complement sensitivity of paroxysmal nocturnal hemoglobinuria bone marrow cells. Blood 1980;55:1040-6.

**10.** Wiedmer T, Hall SE, Ortel TL, Kane WH, Rosse WF, Sims PJ. Complement-induced vesiculation and exposure of membrane prothrombinase sites in platelets of paroxysmal nocturnal hemoglobinuria. Blood 1993;82:1192-6.

**11.** Holguin MH, Fredrick LR, Bernshaw NJ, Wilcox LA, Parker CJ. Isolation and characterization of a membrane protein from normal human erythrocytes that inhibits reactive lysis of the erythrocytes of paroxysmal nocturnal hemoglobinuria. J Clin Invest 1989;84:7-17.

**12.** Kelly RJ, Hill A, Arnold LM, et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. Blood 2011;117:6786-92.

**13.** Loschi M, Porcher R, Barraco F, et al. Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study. Am J Hematol 2016;91:366-70.

**14.** Hill A, Rother RP, Wang X, et al. Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol 2010;149:414-25.

**15.** Hillmen P, Elebute M, Kelly R, et al. Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria. Am J Hematol 2010;85:553-9.

**16.** Risitano AM, Notaro R, Marando L, et al. Complement fraction 3 binding on erythrocytes as additional mechanism of disease in paroxysmal nocturnal hemoglobinuria patients treated by eculizumab. Blood 2009;113:4094-100.

**17.** Hill A, Rother RP, Arnold L, et al. Eculizumab prevents intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria and unmasks low-level extravascular hemolysis occurring through C3 opsonization. Haematologica 2010;95:567-73.

**18.** Risitano AM. Paroxysmal nocturnal hemoglobinuria and the complement system: recent insights and novel anticomplement strategies. Adv Exp Med Biol 2013;735:155-72.

**19.** Risitano AM, Notaro R, Luzzatto L, Hill A, Kelly R, Hillmen P. Paroxysmal nocturnal hemoglobinuria — hemolysis before and after eculizumab. N Engl J Med 2010;363:2270-2.

**20.** Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized phase 2 trial. Ophthalmology 2020;127:186-95.

**21.** Cella D, Lai J-S, Chang C-H, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer 2002;94:528-38.

**22.** Schrezenmeier H, Röth A, Araten DJ, et al. Baseline clinical characteristics and disease burden in patients with paroxysmal nocturnal hemoglobinuria (PNH): updated analysis from the International PNH Registry. Ann Hematol 2020;99:1505-14.

**23.** Morgan BP, Harris CL. Complement, a target for therapy in inflammatory and degenerative diseases. Nat Rev Drug Discov 2015;14:857-77.

**24.** Ricklin D, Lambris JD. Complement in immune and inflammatory disorders: therapeutic interventions. J Immunol 2013;190:3839-47.

**25.** Socié G, Caby-Tosi M-P, Marantz JL, et al. Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10-year pharmacovigilance analysis. Br J Haematol 2019;185:297-310.