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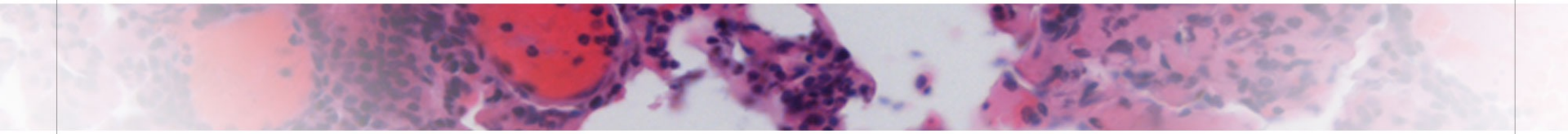

Efficacy and Safety of Pegcetacoplan Treatment in Complement-Inhibitor Naïve Patients with Paroxysmal Nocturnal Hemoglobinuria: Results from the Phase 3 PRINCE Study

Raymond S Wong, MBChB, MD, Juan Ramon Navarro, MD, Narcisa Sonia Comia, MD, Yeow Tee Goh, MBBS, Henry Idrobo, MD, Daolada Kongkabpan, MD, **David Gomez-Almaguer, MD**, Mohammed Al-Adhami, PhD, Temitayo Ajayi, MD, Paulo Alvarenga, MD, PhD, Pascal Deschatelets, PhD, Cedric Francois, MD, PhD, Federico Grossi, MD, PhD, and Teresita Dumagay, MD

Abstract #606

Affiliations

David Gomez-Almaguer, MD: Department of Haematology, University Hospital Dr. José Eleuterio González, Monterrey, Mexico

Raymond S Wong, MBChB, MD: Sir YK Pao Centre for Cancer & Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, Hong Kong

Juan Ramon Navarro, MD: Department of Hematology, Edgardo Rebagliati Hospital, Lima, Peru

Narcisa Sonia Comia, MD: Research Center, 6th Floor Medical Arts Building 3, Mary Mediatrix Medical Center, Lipa, Philippines

Yeow Tee Goh, MBBS: Department of Haematology, Singapore General Hospital, Singapore

Henry Idrobo, MD: Department of Haematology, Julian Coronel Medical Center, Cali, Colombia

Daolada Kongkabpan, MD: Department of Medicine, Songklanagarind Hospital, Songkhla

Mohammed Al-Adhami, PhD: Apellis Pharmaceuticals, Waltham, MA, United States

Temitayo Ajayi, MD: Apellis Pharmaceuticals, Waltham, MA, United States

Paulo Alvarenga, MD, PhD: Apellis Pharmaceuticals, Waltham, MA, United States

Pascal Deschatelets, PhD: Apellis Pharmaceuticals, Waltham, MA, United States

Cedric Francois, MD, PhD: Apellis Pharmaceuticals, Waltham, MA, United States

Federico Grossi, MD, PhD: Apellis Pharmaceuticals, Waltham, MA, United States

Teresita Dumagay, MD: Department of Cellular Therapeutics, Makati Medical Centre, Makati City, Philippines

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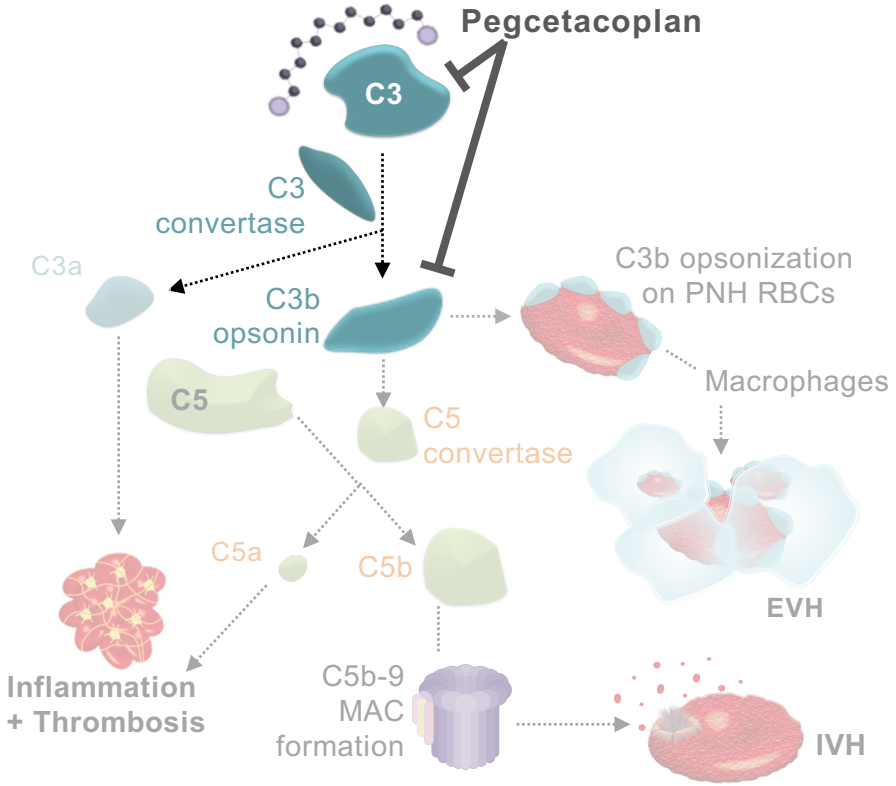
Paroxysmal Nocturnal Hemoglobinuria (PNH) is a Rare and Potentially Life-Threatening Disease Characterized by Complement-Mediated Hemolysis and Thrombosis

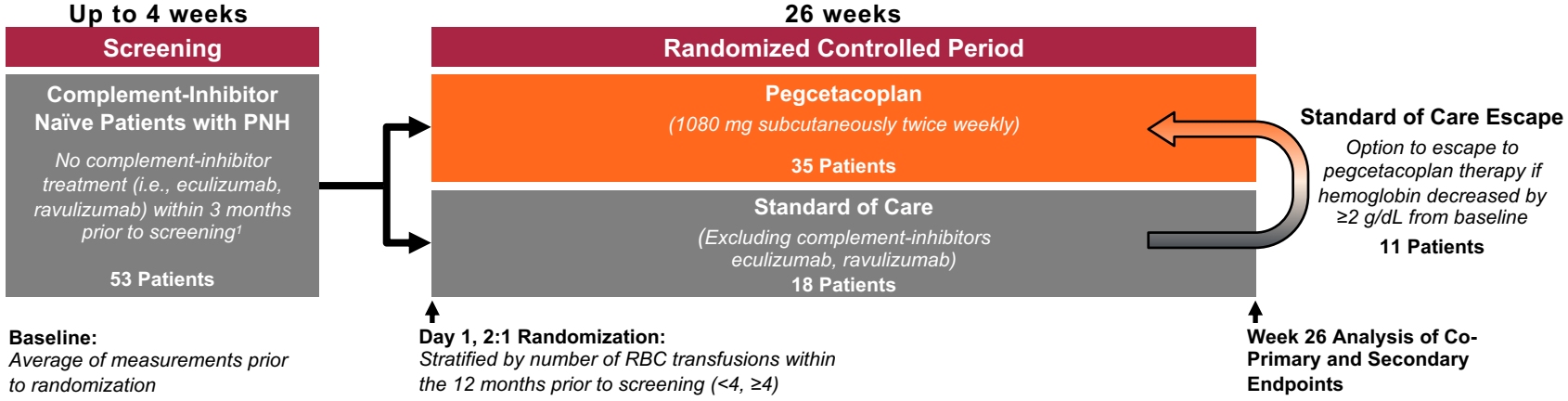
- PNH results in debilitating complement-mediated hemolysis and an increased risk of thrombosis[1]
- Uncontrolled complement activation leads to intravascular hemolysis (IVH), mediated by the membrane attack complex and extravascular hemolysis (EVH), mediated by accumulation of C3 fragments, such as C3b, at the red blood cell surface[2]
  - IVH is associated with increased LDH and reticulocytosis
  - EVH is associated with bilirubinemia and reticulocytosis, without increases in LDH
- Pegcetacoplan, which binds C3 as well as C3b and inhibits C3 cleavage, was approved by the U.S. FDA in May 2021 to treat adults with PNH by controlling IVH and EVH



Abbreviations: EVH, extravascular hemolysis; FDA, Food and Drug Administration; IVH, intravascular hemolysis; LDH, lactate dehydrogenase; MAC, membrane attack complex; PNH, Paroxysmal Nocturnal Hemoglobinuria; U.S., United States

References: 1. DeZern AE, et al. Eur J Haematol. 2013;90(1):16-24. 2. Mastellos DC, et al. Expert Rev Hematol. 2014; 7(5):583–598.

PRINCE: A Phase 3 Study Evaluating the Efficacy and Safety of Pegcetacoplan Compared to Standard of Care in Complement-Inhibitor Naïve Patients with PNH



Study Design	
Population	Patients ≥18 years of age with PNH
Key Eligibility Criteria	• No complement-inhibitor (i.e., eculizumab, ravulizumab) treatment within 3 months prior to screening[a] • Hb levels below the LLN (males: ≤13.6 g/dL; females: ≤12.0 g/dL) • LDH levels ≥1.5 times the ULN (1.5x ULN; ≥339 U/L)
Endpoints	
Co-Primary Endpoints	• Hb stabilization (avoidance of a >1 g/dL decrease in Hb levels in the absence of transfusions through Week 26) • Change from baseline in LDH levels at Week 26
Selected Secondary Endpoints	• Change from baseline in Hb levels at Week 26 • Transfusion avoidance (defined as the proportion of patients who did not require a transfusion or discontinue/escape through Week 26) • Incidence and severity of adverse events (including study deaths) through Week 26

Abbreviations: Hb, hemoglobin; LDH, lactate dehydrogenase; LLN, lower limit of normal; PNH; paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal

[a] All patients screened in PRINCE had never received a complement inhibitor at any point

Summary of Patient Disposition: The Majority of Standard of Care Patients Escaped to the Pegcetacoplan Group; Overall Withdrawal from the PRINCE Study was Minimal

Disposition	PEG (N=35)	SoC (N=18)
Screened	68	
Failed screening	15	
Randomized	35	18
Escape patients to pegcetacoplan group, n (%)	NA	11 (61.1)
Total withdrawn from study, n (%)	2 (5.7)	1 (5.6)
Primary Reason for Withdrawal from Study		
Death[a], n (%)	1 (2.9)	1 (5.6)
Adverse event, n (%)	0	0
Lost to follow-up, n (%)	1 (2.9)	0

[a] The death in SoC arm was due to severe febrile neutropenia; the death in pegcetacoplan arm was due to bone marrow failure and septic shock, both events deemed unrelated to pegcetacoplan

Screening and SoC Escape to Pegcetacoplan Treatment

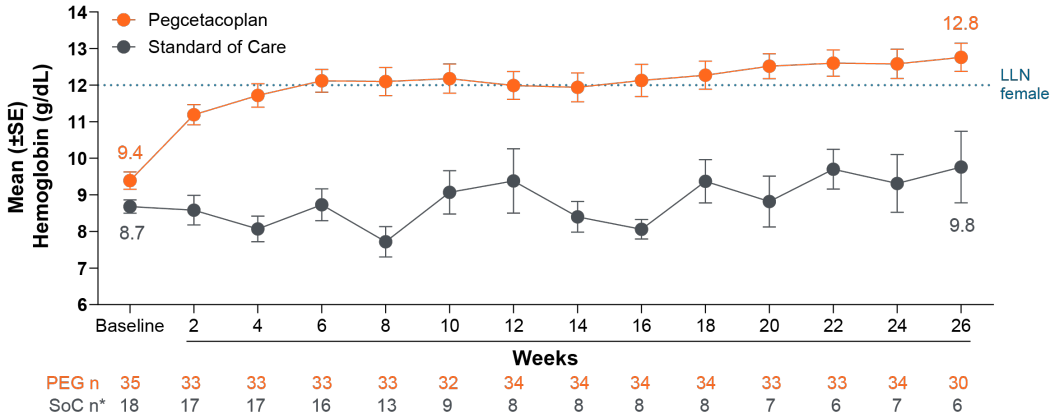
- Out of the 68 individuals screened for the study, 15 (22.1%) failed screening
- Eleven (61.1%) patients from the SoC group escaped to the pegcetacoplan group

Study Withdrawals

- Two (5.7%) pegcetacoplan treated patients and one (5.6%) patient in the SoC group were withdrawn from the study
  - One (2.9%) death occurred in the pegcetacoplan group due to septic shock in the context of bone marrow failure, both events were deemed unrelated to pegcetacoplan
  - One (5.6%) death occurred in the SoC group due to respiratory failure and septic shock
  - One (2.9%) pegcetacoplan-treated patient was lost to follow-up

Abbreviations: NA, not applicable; PEG, pegcetacoplan; SoC, standard of care

Pegcetacoplan was Superior to Standard of Care for the Co-Primary Endpoint of Hemoglobin Stabilization and Led to Greater Improvements in Secondary Endpoints Related to Hemoglobin Levels



*Patients in the standard of care (excluding complement-inhibitors) group had the option to escape to the pegcetacoplan group if their hemoglobin levels decreased by ≥2 g/dL from baseline. All patients that escaped to the pegcetacoplan group from the standard of care group were set to missing in this figure and the presented values from the pegcetacoplan group excludes standard of care escape patients

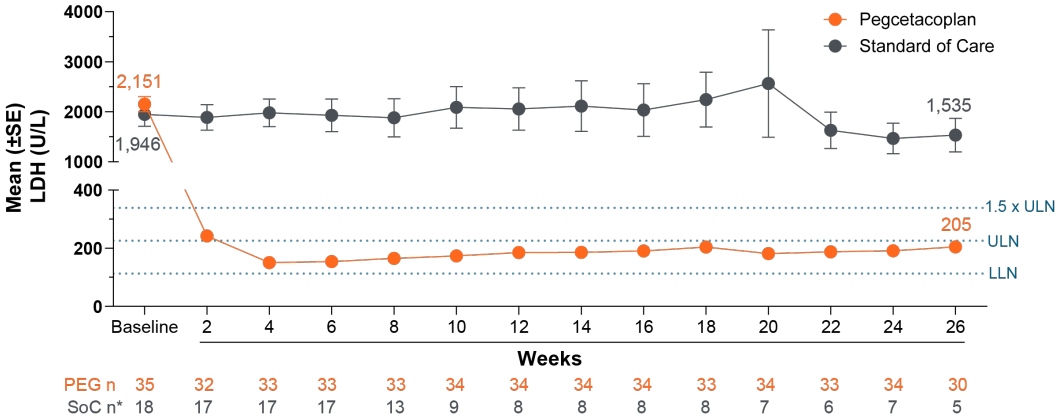
Hemoglobin Stabilization	PEG (N=35)	SoC (N=18)	P-value[a]
Avoidance of >1 g/dL decrease from baseline[b], n (%)	30 (85.7)	0 (0)	<0.0001
Hemoglobin Normalization[c] in the Absence of Transfusions[d]	**PEG (N=35)**	**SoC (N=18)**	**Nominal P-value[a]**
Hb levels ≥ gender-specific LLN[e], n (%)	16 (45.7)	0 (0)	0.0010
Change From Baseline to Week 26 in Hemoglobin Levels	**PEG (N=35)**	**SoC (N=18)**	**P-value[f]**
Hb g/dL, LS Mean (SE)	2.9 (0.4)	0.3 (0.8)	0.0019

[a] Cochran-Mantel-Haenszel Test stratified by number of RBC transfusions within 12 months prior to screening (<4, ≥4)
[b] Avoidance of a >1 g/dL decrease in hemoglobin levels from baseline in the absence of transfusions through Week 26 (Yes/No). Patients who received a transfusion, escaped from SoC to the pegcetacoplan treatment group, withdrew from study, or were lost to follow-up were categorized as non-responders
[c] Hemoglobin Normalization: a hemoglobin level at or above the lower limit of the gender-specific normal range at Week 26 (Yes/No). Patients who received a transfusion, escaped from SoC to the pegcetacoplan treatment group, withdrew from study, or were lost to follow-up were categorized as non-responders
[d] Transfusion: any transfusion of packed RBCs, leukocyte-depleted packed RBCs, leukocyte-poor packed RBCs, leukocyte-poor blood, or whole blood
[e] Males, 13.6 g/dL; females, 12.0 g/dL
[f] ANCOVA model adjusted for treatment, strata, and baseline hemoglobin values

- 85.7% of pegcetacoplan patients achieved hemoglobin stabilization through Week 26 vs 0% in the SoC arm (P<0.0001)
- 45.7% of pegcetacoplan patients achieved hemoglobin normalization through Week 26 vs 0% in the SoC arm (P<0.0010)
- Pegcetacoplan-treated patients experienced a superior change from baseline in hemoglobin levels at Week 26 (P=0.0019), demonstrating a meaningful correction of anemia

Abbreviations: Hb, hemoglobin; LLN, lower limit of normal; LS, least squares; PEG, pegcetacoplan; RBC, red blood cell; SE, standard error; SoC, standard of care

Pegcetacoplan was Superior to Standard of Care for the Co-Primary Endpoint of Change from Baseline in LDH at Week 26 and Led to Greater Improvements in the Secondary Endpoint of LDH Normalization



*Patients in the standard of care (excluding complement-inhibitors) group had the option to escape to the pegcetacoplan group if their hemoglobin levels decreased by ≥2 g/dL from baseline. All patients that escaped to the pegcetacoplan group from the standard of care group were set to missing in this figure and the presented values from the pegcetacoplan group excludes standard of care escape patients

Change From Baseline to Week 26 in LDH Levels	PEG (N=35)	SoC (N=18)	P-value[a]
LDH levels U/L, LS Mean (SE)	-1870.5 (101.0)	-400.1 (312.0)	<0.0001
LDH Normalization[b] in the Absence of Transfusions[c]	**PEG (N=35)**	**SoC (N=18)**	**Nominal P-value[d]**
LDH levels ≤ ULN[e] range, n (%)	23 (65.7)	0 (0)	<0.0001

[a] ANCOVA model adjusted for treatment, strata, and baseline LDH values
[b] LDH normalization is defined as LDH ≤ ULN (226 U/L) of normal range from week 4 to week 26 in the absence of transfusion (Yes/No). Patients who received a transfusion, escaped from SoC to the pegcetacoplan treatment group, withdrew from study, or were lost to follow-up were categorized as non-responders
[c] Transfusion: any transfusion of packed RBCs, leukocyte-depleted packed RBCs, leukocyte-poor packed RBCs, leukocyte-poor blood, or whole blood
[d] Cochran-Mantel-Haenszel Test stratified by number of RBC transfusions within 12 months prior to screening (<4, ≥4)
[e] LDH ULN = 226 U/L

- Significant decreases in LDH levels (P<0.0001) were observed and sustained in pegcetacoplan-treated patients through Week 26
- The secondary endpoint of LDH normalization was achieved by 65.7% of patients in the pegcetacoplan group as demonstrated by LDH levels below the upper limit of normal through Week 26 vs 0% in the SoC arm (P<0.0001)
- Change from baseline in LDH levels suggest that pegcetacoplan treatment contributed to comprehensive and persistent control of hemolysis

Abbreviations: LDH, lactate dehydrogenase; LS, least squares; PEG, pegcetacoplan; RBC, red blood cell; SE, standard error; SoC, standard of care; ULN, upper limit of normal

Pegcetacoplan was Superior to Standard of Care for the Secondary Endpoint of Transfusion Avoidance

- Pegcetacoplan demonstrated statistical superiority in transfusion avoidance compared to SoC (P<0.0001), indicating significant alleviation in transfusion burden
- Patients in the pegcetacoplan group were transfused with 0.6 median units through Week 26, which was significantly lower than the 3.3 median units transfused in the SoC group (P<0.0001)
- Composite analysis of both transfusion requirement and hemoglobin drop was performed to overcome possible bias of patients in the SoC group escaping prior to receiving transfusion
    - A small proportion (11.4%) of pegcetacoplan-treated patients vs 100% SoC patients met one or both criteria (P<0.0001)

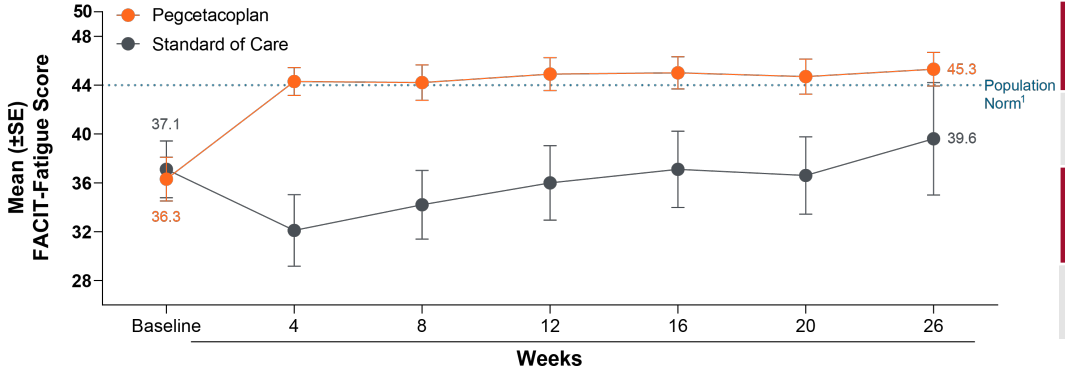
Patients treated with pegcetacoplan required fewer transfusions and did not experience hemoglobin level decreases, demonstrating **effective management of hemoglobin levels**

Transfusion Avoidance[a]	**PEG (N=35)**	**SoC (N=18)**	**P-value[b]**
Yes (avoided transfusions), n (%)	32 (91.4)	1 (5.6)	<0.0001
Total Number of Transfusion Units[c]	**PEG (N=35)**	**SoC (N=18)**	**P-value[d]**
Total Units	21	59	
Median Units	0.6	3.3	<0.0001
Number of Patients Who Received a Transfusion OR had a Decrease in Hb >2 g/dL from Baseline	**PEG (N=35)**	**SoC (N=18)**	**P-value[b]**
Yes[e] (received transfusion or had Hb decrease >2g/dL), n (%)	4 (11.4)	18 (100.0)	<0.0001

[a] Transfusion avoidance is defined as the proportion of subjects who do not require a transfusion through Week 26 (Yes/No). Patients who received a transfusion, escaped from SoC to the pegcetacoplan treatment group, withdrew from study, or were lost to follow-up were categorized as non-responders
[b] Cochran-Mantel-Haenszel Test stratified by number of RBC transfusions within 12 months prior to screening (<4, ≥4)
[c] Total Number of Transfusion Units Transfused During Randomized Controlled Period. Transfusion: any transfusion of packed RBCs, leukocyte-depleted packed RBCs, leukocyte-poor packed RBCs, leukocyte-poor blood, or whole blood
[d] Wilcoxon Rank-Sum Test, median difference P-value
[e] Patients who received a transfusion through Week 26, had a decrease in hemoglobin levels >2 g/dL from baseline, escaped from the standard of care group to the pegcetacoplan treatment group, withdrew from the study, or were lost to follow-up were categorized as "Yes"

Abbreviations: Hb, hemoglobin; PEG, pegcetacoplan; RBC, red blood cell; SE, standard error; SoC, standard of care

Patients Treated with Pegcetacoplan Achieved Clinically Meaningful Improvements in FACIT-Fatigue Scores that are Consistent with Improved Hematologic Parameters and Transfusion Avoidance



*Patients in the standard of care (excluding complement-inhibitors) group had the option to escape to the pegcetacoplan group if their hemoglobin levels decreased by ≥2 g/dL from baseline. All patients that escaped to the pegcetacoplan group from the standard of care group were set to missing in this figure and the presented values from the pegcetacoplan group excludes standard of care escape patients

Change From Baseline to Week 26 in FACIT-Fatigue Score	PEG (N=35)	SoC (N=18)	P-value[a]
FACIT-Fatigue Score, LS Mean (SE)	7.8 (1.2)	3.3 (2.1)	0.0610
FACIT-Fatigue Score Clinically Meaningful Improvement[b] in the Absence of Transfusions[c]	**PEG (N=35)**	**SoC (N=18)**	**Nominal P-value[d]**
Clinically meaningful[b] FACIT-Fatigue score improvement, n (%)	21 (60.0)	2 (11.1)	0.0007

[a] ANCOVA model adjusted for treatment, strata, and baseline FACIT-Fatigue values
[b] Clinically meaningful improvement is defined as achieving a (≥3-point increase)[2] in FACIT-Fatigue score from baseline to Week 26 (Yes/No). Patients who received a transfusion, escaped from SoC to the pegcetacoplan treatment group, withdrew from study, or were lost to follow-up were categorized as non-responders
[c] Transfusion: any transfusion of packed RBCs, leukocyte-depleted packed RBCs, leukocyte-poor packed RBCs, leukocyte-poor blood, or whole blood
[d] p-value based on unadjusted post hoc analysis

- The pegcetacoplan group showed clinically meaningful improvements in FACIT-Fatigue (≥3-point increase[2]) scores through Weeks 4-26 that were numerically greater than the improvements seen in the SoC group
  - Although there was a trend toward significance (P=0.0610), the mean difference between groups at Week 26 was not statistically significant, possibly due a small sample size and high variability in the SoC group after many patients (61.1%) escaped to the pegcetacoplan group as well as the pegcetacoplan group reaching the normal, healthy adult score (ceiling effect) for the FACIT-Fatigue scale

Abbreviations: FACIT, Functional Assessment of Chronic Illness Therapy; PEG, pegcetacoplan; RBC, red blood cell; SD, standard deviation; SoC, Standard of Care.
References: 1. Montan I, et al. Value Health. 2018 Nov;21(11):1313-1321. 2. Cella D, et al. J Pain Symptom Manage. 2002;24(6):547-561

Safety and Efficacy Data Demonstrate a Positive Risk-Benefit Profile for Pegcetacoplan through Week 26 of the PRINCE trial

Adverse Events	Overall PEG[a] (n=46)	Overall SoC[b] (n=18)
Any AE, n (%)	33 (71.7)	12 (66.7)
AEs Related to PEG	13 (28.3)	NA
Serious AEs, n (%)	4 (8.7)	3 (16.7)
Serious AEs Related to PEG	0 (0)	NA
AE by Severity, n (%)		
Mild or Moderate	29 (63.1)	10 (55.6)
Severe	4 (8.7)	2 (11.1)
Most Common TEAEs, n (%)		
Injection site reaction	14 (30.4)	0 (0)
Hypokalemia	6 (13.0)	2 (11.1)
Dizziness	5 (10.9)	0 (0)
Fever	4 (8.7)	0 (0)

[a] Overall PEG includes the original pegcetacoplan group (n=35) and the patients that received pegcetacoplan treatment upon escape from the SoC group to the pegcetacoplan group (n=11)
[b] Overall SoC includes any adverse event that occurred on or prior to escape to PEG; after the escape to PEG the event was counted in the overall PEG column

Study Deaths and Serious Adverse Events

- No deaths or serious adverse events deemed related to pegcetacoplan occurred
- Two deaths unrelated to the study drug occurred
  - Pegcetacoplan group: one death due to septic shock in the context of bone marrow failure
  - SoC group: one death due to respiratory failure and septic shock

Other Adverse Events

- Most adverse events in the pegcetacoplan group were of mild (34.8%) or moderate (28.3%) severity
- Only 8.7% of total adverse events in the pegcetacoplan group were reported as severe
- Overall, there were no pegcetacoplan-related adverse events leading to drug or study discontinuation
- No events of acute hemolysis were observed in either treatment group through Week 26

Abbreviations: AE, adverse event; NA, not applicable; PEG, pegcetacoplan; SoC, standard of care; TEAE, treatment emergent adverse event

Conclusions

Patients with PNH that were naïve to complement-inhibitor treatment displayed meaningful hematologic and clinical improvements throughout 26 weeks of pegcetacoplan treatment, as demonstrated by:

- Improved hemoglobin levels, lactate dehydrogenase levels, and transfusion avoidance
- Improvements in quality of life (improved FACIT-Fatigue scores)

The safety profile of pegcetacoplan was similar to results from previous studies, suggesting a favorable risk-benefit profile

- There were no drug discontinuations due to pegcetacoplan-related adverse events

These results emphasize the potential of pegcetacoplan to provide disease control for adults with PNH that are naïve to complement-inhibitor therapy

For further investigations into pegcetacoplan and PNH, please visit the following poster presentations:

- Hematologic response and quality of life correlation following pegcetacoplan treatment (PEGASUS, PADDOCK/PALOMINO studies) **(Abstract #1104)**
- Pegcetacoplan treatment in patients with PNH and baseline hemoglobin levels ≥10 g/dL **(Abstract #2194)**
- A long-term safety and efficacy extension study of pegcetacoplan in patients with PNH **(Abstract #2175)**
- Changes in hemoglobin levels observed in patients with PNH receiving treatment with C5-inhibitors eculizumab or ravulizumab **(Abstract #1112)**

Abbreviations: FACIT, Functional Assessment of Chronic Illness Therapy; PNH, Paroxysmal Nocturnal Hemoglobinuria

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