# Reduced iron overload with pegcetacoplan treatment in eculizumab-experienced patients with paroxysmal nocturnal hemoglobinuria

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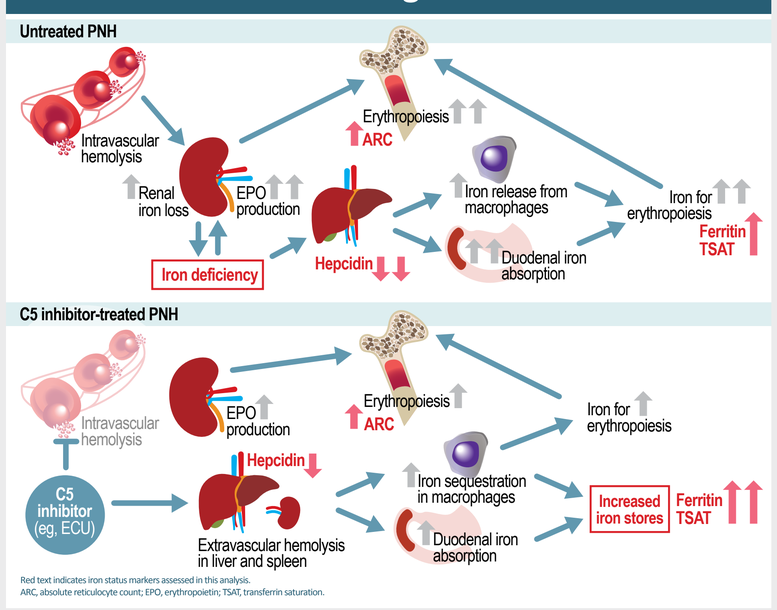
## CONCLUSIONS

- ✓ Iron overload (ie, serum transferrin saturation >50%) resolved with pegcetacoplan in ≥70% of patients with PNH who had ongoing anemia and baseline iron overload on eculizumab
- ✓ Normalization of transferrin saturation with pegcetacoplan suggest that extravascular hemolysis (EVH) control and improved anemia with pegcetacoplan can improve iron regulation
- ✓ Ongoing EVH may explain the high ferritin concentrations observed with complement C5 inhibitors. Persistently high ferritin concentrations may reflect that 32 weeks may be too short to observe changes in iron stores.
- ✓ Resolution of iron overload can be rapid as transferrin saturation <50% was often reported at week 20, the earliest timepoint assessed
- ✓ Resolution of iron overload was accompanied by hepcidin increase and absolute reticulocyte count (ARC) decrease. These changes were also reported at week 20.
- ✓ Patients with iron overload that did not resolve with pegcetacoplan had greater transfusion needs before the trial and 2 had a substantial transfusion burden during the trial; the higher underlying disease activity and/or increased transfusion needs could have contributed to ongoing iron overload

## INTRODUCTION

- In untreated paroxysmal nocturnal hemoglobinuria (PNH), renal iron loss from uncontrolled IVH leads to iron deficiency and increased erythropoiesis, which decreases the release of hepcidin (a negative regulator of iron) from the liver[1,2] (**Figure 1**)
  - Decreased hepcidin increases iron absorption and enhances iron release from macrophages, potentially increasing iron for red blood cell production to make up for the red blood cells lost to intravascular hemolysis (IVH)[2]
- Complement C5 inhibitors, such as eculizumab, relieve IVH in PNH but could lead to EVH and transfusion-dependent anemia from ongoing transfusion requirements, causing transfusional iron overload and possible iron retention in the Kupffer cells of the liver[2–4] (**Figure 1**)
  - Increased erythropoiesis due to EVH can also reduce hepcidin concentrations and consequently enhance iron absorption, furthering iron overload[1,2]
  - Increased ferritin, a hallmark of iron overload, can occur with complement C5 inhibitors, even without transfusions[1]

**Figure 1. Potential effects of complement C5 inhibitors for PNH on iron regulation[2]**




Red text indicates iron status markers assessed in this analysis.
ARC, absolute reticulocyte count; EPO, erythropoietin; TSAT, transferrin saturation.

- In the Phase 3 PEGASUS trial (NCT03500549), pegcetacoplan, a complement C3-targeted therapy, increased hemoglobin concentrations and reduced transfusion requirements in patients with PNH who had received eculizumab for an average of 3–4 years[5]
- In the year before trial entry, approximately 75% of PEGASUS patients required a transfusion

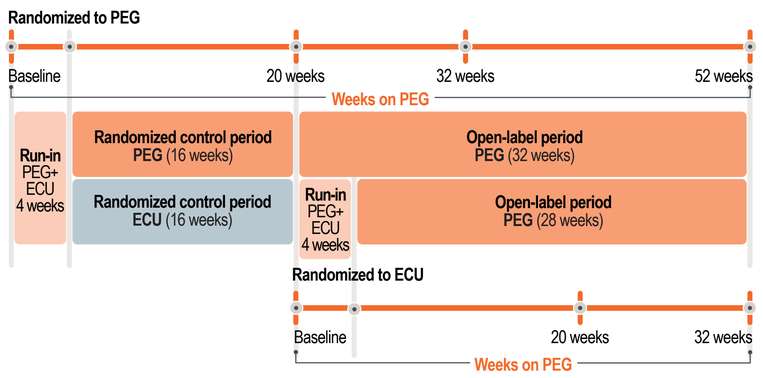
## OBJECTIVE

**To compare markers of iron overload in PEGASUS patients before and during pegcetacoplan treatment**

## METHODS

- In PEGASUS, adults with PNH who had residual anemia with C5 inhibitor treatment received eculizumab and pegcetacoplan for 4 weeks (run-in), followed by eculizumab or pegcetacoplan monotherapy for 16 weeks (to week 20) (**Figure 2**)
  - In the subsequent 32-week open-label period, patients either continued pegcetacoplan (for a total pegcetacoplan treatment duration of up to 52 weeks) or switched from eculizumab to pegcetacoplan for up to 32 weeks of pegcetacoplan
- In the current analysis, baseline was prior to run-in for pegcetacoplan-randomized patients and at week 20 (prior to pegcetacoplan initiation) for the eculizumab-randomized patients (**Figure 2**)
  - Patients with serum transferrin saturation >50% were defined as having iron overload[6]
  - Transfusion history and iron parameters (transferrin, ferritin, hepcidin, ARC) were compared relative to baseline iron overload status after 20 and 32 weeks of pegcetacoplan treatment
  - Patients did not fast before blood sampling

**Figure 2. Study design for the PEGASUS trial and the iron parameters analysis**



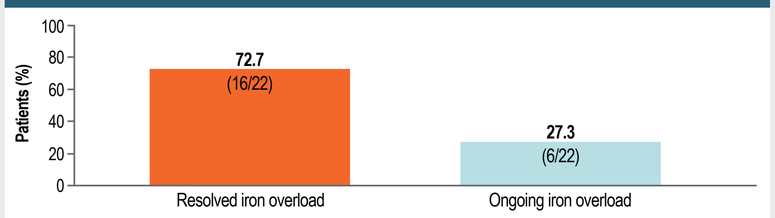

ECU, eculizumab; PEG, pegcetacoplan.

## RESULTS

- In PEGASUS, 27 of 80 (33.8%) evaluable patients had baseline iron overload
  - These 27 patients had a mean (standard deviation [SD]) baseline transferrin saturation of 64.6% (11.4%)
  - Twenty-one had received ≥4 transfusions the year prior
- In the year before PEGASUS, patients receiving eculizumab who had baseline iron overload had a mean of 10.8 transfusions versus 6.4 for patients without baseline iron overload
- Iron overload resolved within 52 weeks of pegcetacoplan treatment in 16 of 22 (72.7%) patients with baseline iron overload and post-baseline iron overload data; iron overload had not resolved in 6 patients (27.3%) (**Figure 3**). Of the 16 patients with resolved iron overload, a majority experienced resolution after 20 weeks of pegcetacoplan treatment (n=10); these patients had a mean (standard deviation [SD]) transferrin saturation of 34.9% [6.0%]) at week 20. Four patients had iron overload resolution at 32 weeks (mean [SD] transferrin saturation, 32.9% [10.1%]), 1 had resolution at 40 weeks (transferrin saturation, 47.6%), and 1 had resolution at 52 weeks (transferrin saturation, 39.7%).

## RESULTS *(cont.)*

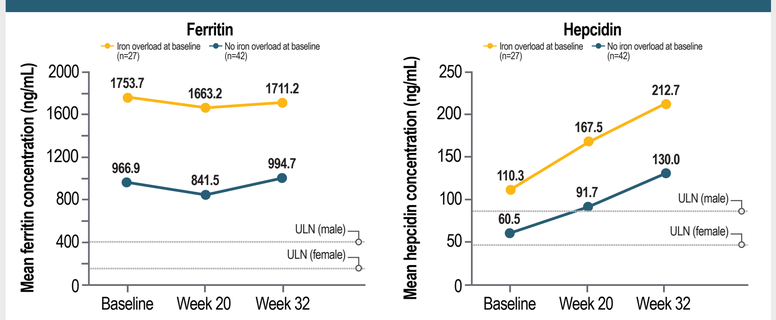
**Figure 3. Resolution of iron overload after up to 52 weeks of pegcetacoplan treatment for PNH[a]**




[a]Baseline iron overload was defined as a transferrin saturation of >50% at baseline. Only patients with evaluable iron overload data at both baseline and after the specified durations of pegcetacoplan treatment were included.
PNH, paroxysmal nocturnal hemoglobinuria.

- Patients with baseline iron overload had higher ferritin and hepcidin concentrations than patients without baseline iron overload (**Figure 4**)
- Hepcidin concentrations increased with pegcetacoplan regardless of iron overload status (**Figure 4**)

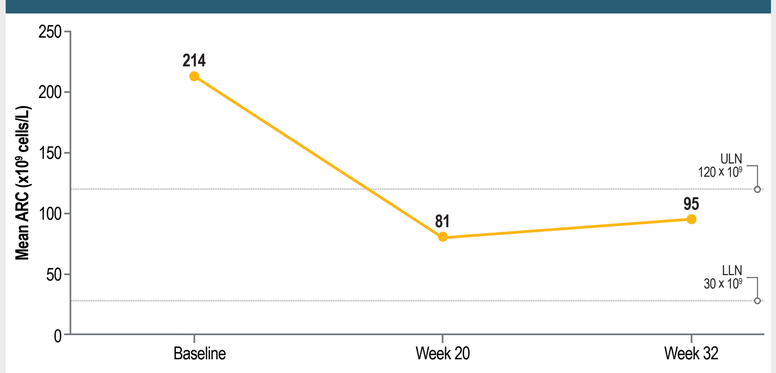
**Figure 4. Concentrations of ferritin and hepcidin in eculizumab-experienced patients with PNH before and after pegcetacoplan treatment, by baseline iron overload status[a]**




[a]Baseline iron overload was defined as a transferrin saturation of >50% at baseline.
ARC, absolute reticulocyte count; PNH, paroxysmal nocturnal hemoglobinuria; ULN, lower limit of normal; ULN, upper limit of normal.

- In patients with baseline iron overload, mean ARC decreased from above normal at baseline to within normal limits after 20 or 32 weeks of pegcetacoplan treatment (**Figure 5**)

**Figure 5. ARC before and after pegcetacoplan treatment in eculizumab-experienced patients with PNH and baseline iron overload (n=26)[a]**




[a]Baseline iron overload was defined as a transferrin saturation of >50% at baseline.
PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal.

**REFERENCES:** **1.** Waheed A, Kuter DJ. *Am J Hematol*. 2021;96(7):E235–E237. **2.** Schaap CCM, et al. *Hemasphere*. 2023;7(5):e878. **3.** Hill A, et al. *Blood*. 2005;106(7):2559-2565. **4.** Hill A, et al. *Haematologica*. 2010;95(4):567–573. **5.** Hillmen P, et al. *N Engl J Med*. 2021;384(11):1028–1037. **6.** European Association for the Study of the Liver. *J Hepatol*. 2022;77(2):479–502.

**Abbreviations:** ARC, absolute reticulocyte count; ECU, eculizumab; EPO, erythropoietin; EVH, extravascular hemolysis; IVH, intravascular hemolysis; LLN, lower limit of normal; PNH, paroxysmal nocturnal hemoglobinuria; PEG, pegcetacoplan; SD, standard deviation; ULN, upper limit of normal.

**Acknowledgments:** This study was funded by Apellis Pharmaceuticals, Inc. Writing and editorial support was provided by Kathryn Fogarty, PhD, (Kay Square Scientific, Newtown Square, PA, USA). This support was funded by Apellis Pharmaceuticals, Inc., and Sobi (Swedish Orphan Biovitrum AB). Apellis Pharmaceuticals and Sobi reviewed the poster.

**Prior publication:** Data published in part in Shammo J, et al. *Blood*. 2024;144[suppl 1]:5677–5678. https://doi.org/10.1182/blood-2024-203271

**Disclosures:** **JS** received consultancy fees from Alexion/AstraZeneca, BMS, GSK, Sobi, Omeros, Regeneron, and Novartis; and serves on DSMB for Apellis. She received research funding from Protagonist pharma, Alexion, and Incyte. **DK** received research funding from Alnylam, Biocryst, Novartis, Rigel, Sanofi (Principia), Takeda (Bioverativ), and UCB; and consulting fees from AIRx, Alexion (Syntimmune), Alnylam, Alpine, Amgen, Argenx, BioCryst, Bristol Myers Squibb (BMS), Caremark, Cellularity, Cellphire, Chugai, CRICO, Daiichi Sankyo, Dianthus, Electra Therapeutics, Fuji, Hemopure, Hengrui, Immunovant, Incyte, Inmagenebio, Kezar, Kyowa-Kirin, Merck Sharp Dohme, Momenta, Novartis, Nuvig, Pfizer, Platelet Biogenesis, Platelet Disorder Support Association, Protagonist, Rigel, Sanofi (Bioveratif), Sanofi (Principia), Sanofi (Genzyme), Sobi (Dova), Takeda, UCB, Up-To-Date, and Zafgen. **PH** is an employee of Apellis and holds stock or stock options. **MY** was an employee of Apellis at the time of the study.

**2nd International PNH Interest Group (IPIG) Conference**
**May 15–16, 2025 | Paris, France**

**Data previously published:** Jamile Shammo, Michael Yeh, Peter Hillmen, David J Kuter; Reduced Iron Overload with Pegcetacoplan Treatment in Eculizumab-Experienced Patients with Paroxysmal Nocturnal Hemoglobinuria. *Blood* 2024; 144 (Supplement 1): 5677. doi: https://doi.org/10.1182/blood-2024-203271