

Improvement in Iron Overload With Pegcetacoplan Therapy in Patients With Paroxysmal Nocturnal Hemoglobinuria Previously Treated With Eculizumab

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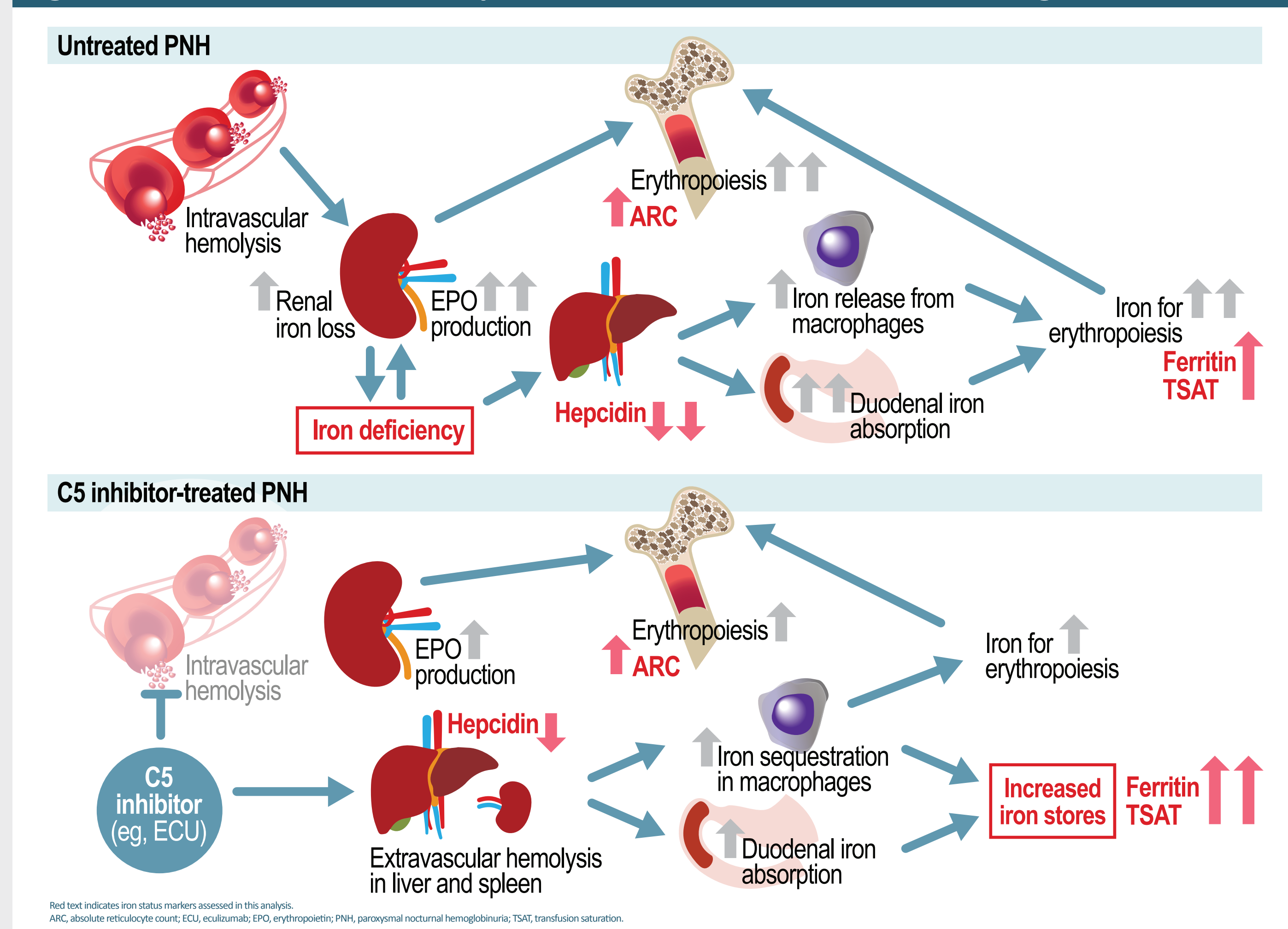
CONCLUSIONS

- ✓ Iron overload (ie, serum transferrin saturation >50%) resolved with pegcetacoplan in ≥50% of patients with PNH who had ongoing anemia and baseline iron overload on eculizumab
- ✓ Persistently high ferritin concentrations in eculizumab-experienced patients during 32 weeks of pegcetacoplan may reflect that this period was too short to observe changes in this surrogate marker
- ✓ Normalization of transferrin saturation and increased hepcidin 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

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 liver²⁻⁴ (**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 transfusions¹

Figure 1. Potential effects of complement C5 inhibitors for PNH on iron regulation²



- 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 years⁵
- In the year before trial entry, approximately 75% of PEGASUS patients required a transfusion, likely due to EVH⁵

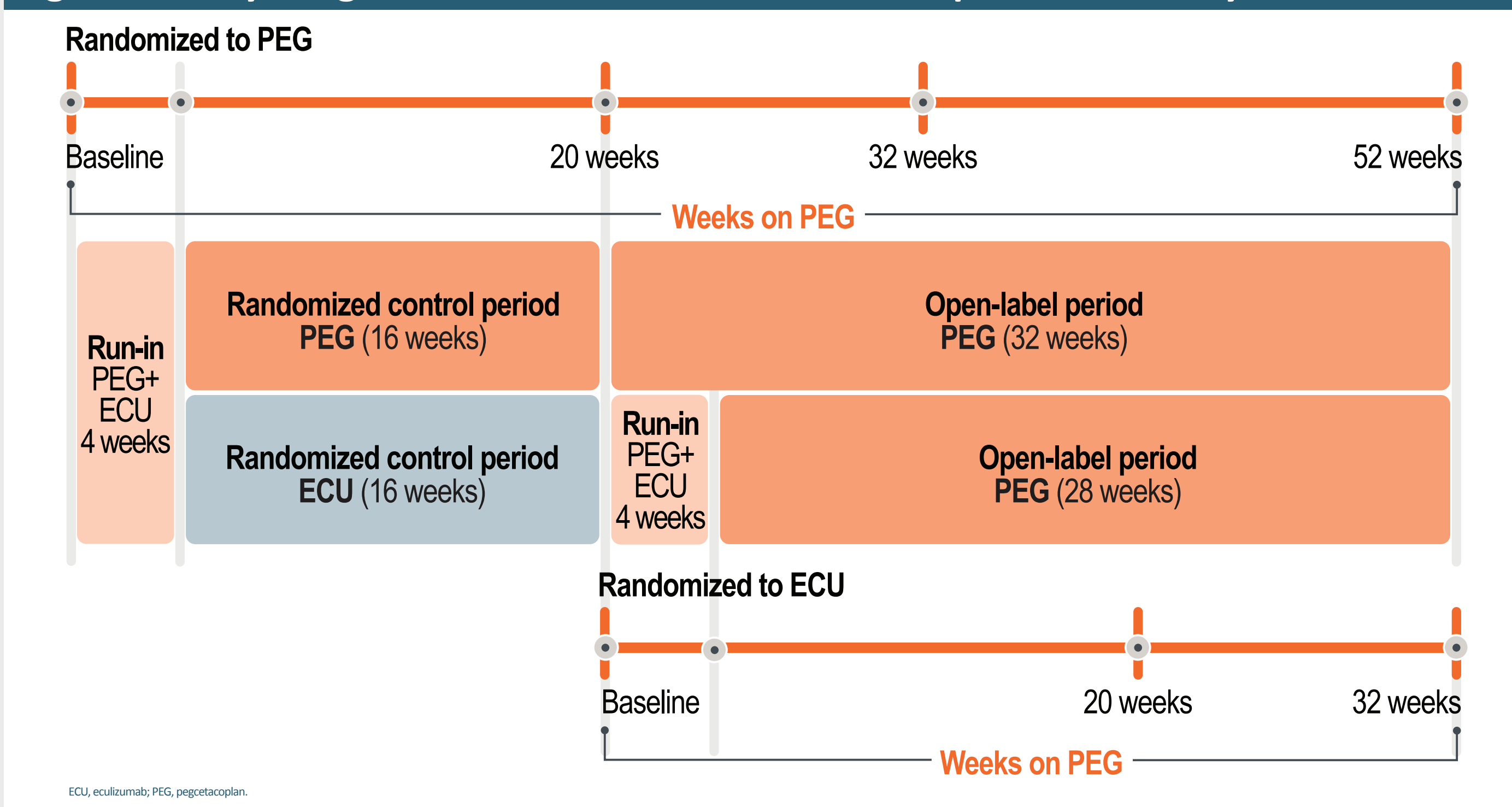
OBJECTIVE

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 overload⁶
 - Transfusion history and iron parameters (transferrin, ferritin, hepcidin, absolute reticulocyte count [ARC]) were compared relative to baseline iron overload status
 - Patients did not fast before blood sampling

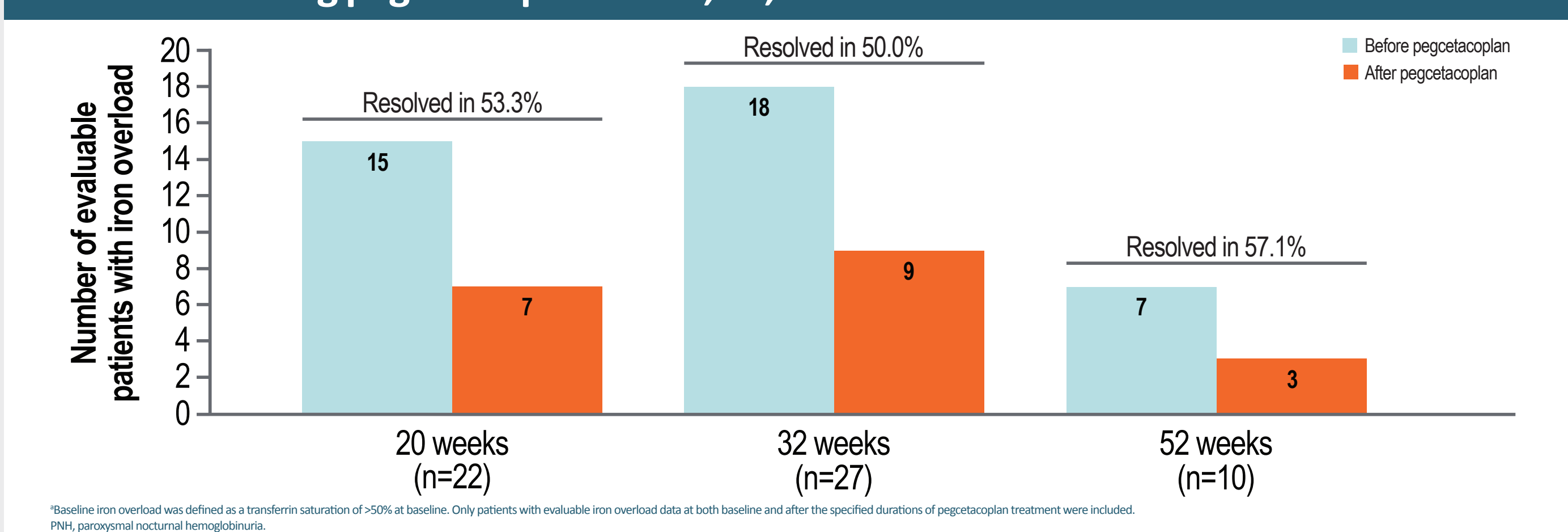
Figure 2. Study design for the PEGASUS trial and the iron parameters analysis



RESULTS

- In PEGASUS, 27 of 69 (39.1%) evaluable patients had baseline iron overload
- In the year before PEGASUS, patients receiving eculizumab who had baseline iron overload had a mean (SD) of 10.6 (8.9) transfusions versus 4.9 (4.9) for patients without baseline iron overload
- After 20, 32, and 52 weeks of pegcetacoplan, iron overload resolved (ie, transferrin saturation fell to ≤50%) in approximately half of the evaluable patients with baseline iron overload (**Figure 3**)

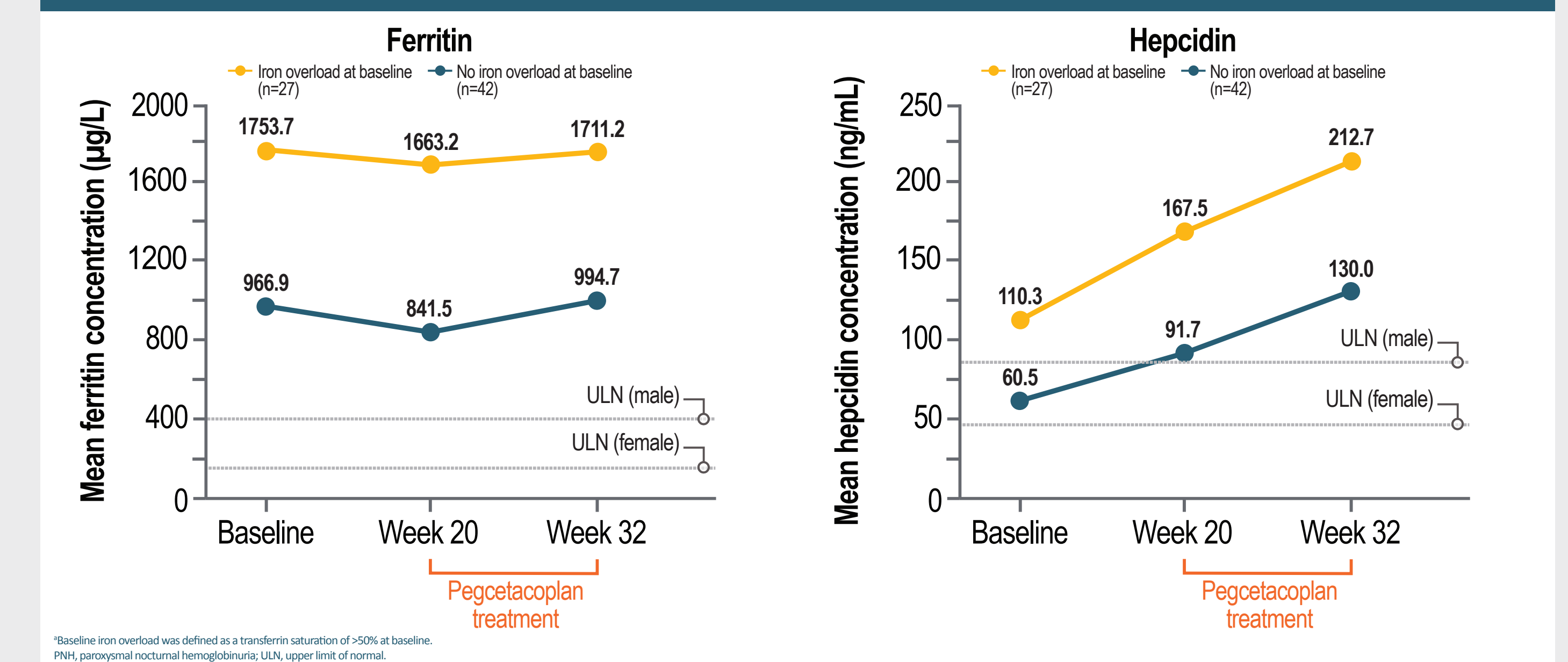
Figure 3. Number of eculizumab-experienced patients with PNH with iron overload before and after receiving pegcetacoplan for 20, 32, or 52 weeks^a



RESULTS (continued)

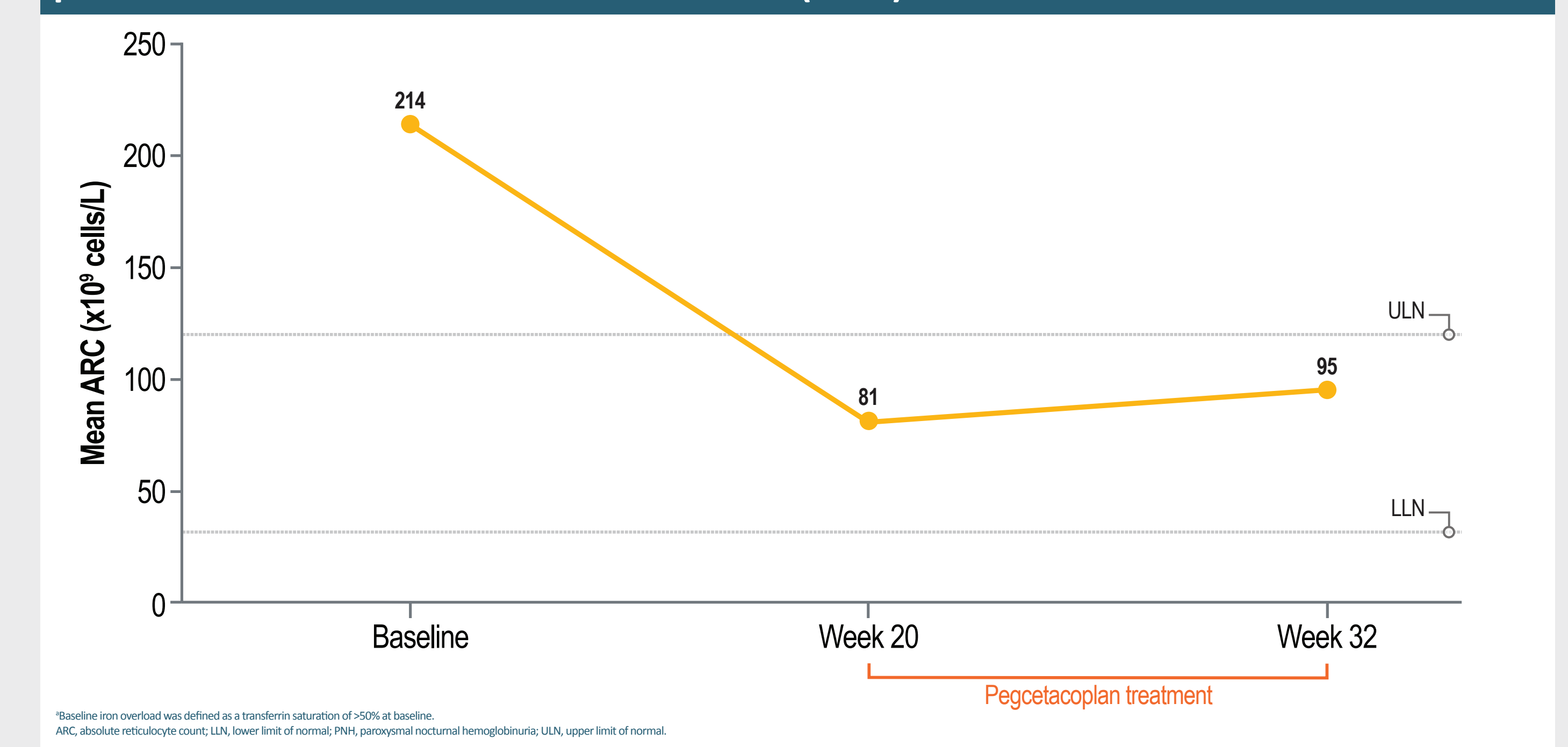
- Patients with baseline iron overload had higher ferritin and hepcidin concentrations than patients without baseline iron overload (**Figure 4**)
- Hepcidin concentrations increased with pegcetacoplan regardless of iron overload status, although patients with baseline iron overload had higher baseline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



- 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=27)^a



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Abbreviations:

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

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